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THIRD SERIES FOUNDED BY EDWARD JACKSON

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DEPARTMENTS

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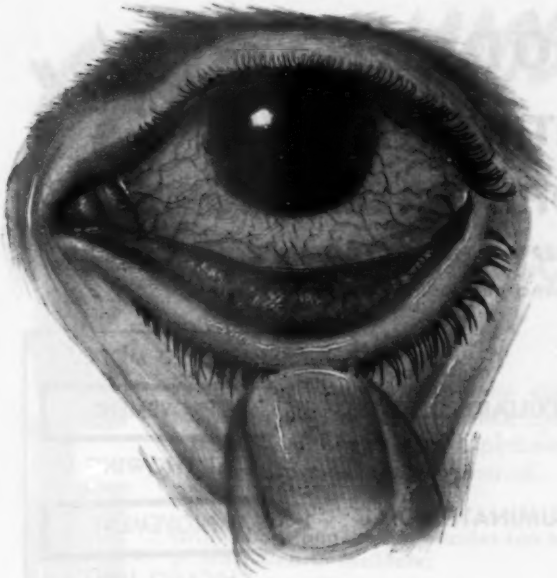

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AMERICAN JOURNAL OF OPHTHALMOLOGY

VOLUME 34 SEPTEMBER, 1951 NUMBER 9

THE ETIOLOGY AND TREATMENT OF PHLYCTENULAR KERATOCONJUNCTIVITIS*

THE ESTELLE L. DOHENY LECTURE

PHILLIPS THYGESON, M.D.
San Jose, California

It is indeed an honor to have been invited to give this, the third Doheny Lecture, and a privilege to follow my two distinguished colleagues, Dr. Alan C. Woods and Dr. C. S. O'Brien, in this lecture series. I have, of course, been a profoundly interested spectator of the work of the Doheny Foundation since it began and have shared the hope, and indeed the conviction, of its founder, Mrs. Estelle L. Doheny, that it will contribute increasingly to ophthalmology and to the welfare of the people of California and the West.

My contribution to this lecture series must of necessity be modest, but the subject I have chosen seems to me to be an important one since it concerns primarily the vision of our children, and particularly of the children of the economically depressed areas of this country and of the world. Furthermore, as we shall see later, the subject has very special interest as an example of bacterial allergy, a disease mechanism with wide application in ophthalmology, particularly in relation to uveitis.

Phlyctenular keratoconjunctivitis has been known under a wide variety of names. These include, on the one hand, those referable to the cornea, such as scrofulous keratitis, impetiginous keratitis, eczematous keratitis, and strumous keratitis; and on the other hand, those referable to the conjunctiva, such as conjunctivitis-lymphatica, -scrofulosa, -phlyctenulosa, -pustulosa, -exanthematica, and herpes conjunctivae (Stellwag). Of all of these the names, "eczematous keratitis" or "eczematous conjunctivitis," and "phlyctenular keratitis" or "phlyctenular ophthalmia" have been used most commonly. Fuchs popularized the term "conjunctivitis eczematosa" in his textbook, but in view of our dependence upon the phlyctenule for diagnosis, the terms "phlyctenular keratoconjunctivitis" or "phlyctenular ophthalmia" would seem to be more appropriate.

Phlyctenular ophthalmia is an old disease. Crude descriptions of it are to be found in the Greek and Arabic literature, but St. Yves,[1] in his textbook published in 1722, seems to have been one of the first to define a nodular conjunctivitis with the characteristics of the disease.

Wardrop,[2] in his *Essays on the Morbid Anatomy of the Human Eye*, which appeared in 1808, depicted the clinical appearance of the disease in one of his plates. In 1869, Iwanoff[3] reported the first histologic studies of the phlyctenule, and in 1880 Horner[4] drew attention to the close association of the disease with eczematous lesions of the face.

The association of phlyctenulosis with so-called "scrofulous diathesis" was also noted by many of the early observers and, when

* From the Francis I. Proctor Foundation for Research in Ophthalmology and the Division of Ophthalmology, University of California School of Medicine, San Francisco.

scrofula was finally identified with tuberculosis, an attempt was made to establish phlyctenulosis as a strictly tuberculous manifestation. However, the invariable failure of early workers to isolate tubercle bacilli from the phlyctenule, and the absence of a clear histologic picture of tuberculosis in any of the phases of the disease, led bacteriologists to look for other bacteria.

The extraordinary consistency with which Staphylococcus aureus was isolated from the conjunctivas of phlyctenulosis patients led a number of workers to consider the disease to be a staphylococcic manifestation. Others were led astray by the favorable effect of dietary treatment to consider the disease as due to vitamin deficiency or to a disturbance in the carbohydrate metabolism.

With the introduction of the tuberculin test by von Pirquet in 1907, the significance of tuberculosis in phyctenulosis again became apparent and was emphasized by the frequent occurrence of phlyctenules in the keratoconjunctivitis produced by the ophthalmic tuberculin test of Calmette and Wolff-Eisner. It was suggested that the phlyctenule was an allergic response to circulating tuberculous products in a patient with minimal tuberculosis, and this is the theory of etiology which has to date received the widest acceptance. In 1930, however, Goldenburg[5] flatly denied the role of tuberculosis in phlyctenulosis and, as recently as 1948, Stern and Landau[6] incriminated ariboflavinosis as the cause of the disease.

My own interest in phlyctenular keratoconjunctivitis was first aroused by its high incidence among the Apache Indians of Arizona, which I observed in the course of a series of trachoma studies during the years 1934 to 1938, and among the Negro and Puerto Rican children of New York City prior to the onset of World War II. A study of the disease in these children was begun at that time but was interrupted by the war.

In 1948, I noted the report[7] of Fields, a member of an American Medical Association investigating committee, which stated that from 20 to 50 percent of the children in many Alaskan native villages had corneal scars due to phlyctenulosis. In that same year Dr. M. H. Fritz of Anchorage, Alaska, and Dr. Jack C. Haldeman of the United States Public Health Service, called my attention to the extraordinary incidence of corneal scars caused by this disease among the Indian, Aleut, and Eskimo children of Alaska.

In the summers of 1949 and 1950, I participated with Dr. Fritz and Dr. Davis Durham[8] in a study of the disease at the Mt. Edgecumbe native school near Sitka, Alaska. From the preliminary reports of this study, which was sponsored by the United States Public Health Service in coöperation with the Alaskan Native Service and the Territorial Health Department, I have drawn material for comparison with data which have been reported in the domestic and foreign literature.

Importance of Phlyctenular Ophthalmia as a Cause of Lowered Visual Acuity and Blindness

When I began the study of ophthalmology in 1928, phlyctenular ophthalmia was a common disease in the eye clinic of the University of Colorado Medical School. Since that time, I have been struck by the reduction in the incidence and severity of the disease in the white population of the United States. In spite of this reduction, however, which according to reports from numerous clinics throughout the world has been widespread, I continue to see children, and occasionally adults, with severe forms of the disease, both in private practice and in the eye clinic of the University of California Medical School.

Reports indicate that in Europe a recrudescence of the disease coincided with the outbreak of World War II. In Greece, phlyctenulosis has been cited as the eye lesion most commonly seen in the University Clinic at Athens, and in China it has been in-

FIG. 1

FIG. 2

FIG. 3

FIG. 4

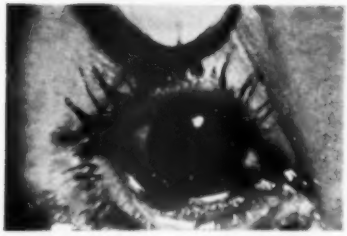

FIG. 5

FIG. 6

FIGS. 1 TO 6 (THYGESON). (FIG. 1) PHLYCTENULE AT THE LIMBUS. (FIG. 2) PALPEBRAL PHLYCTENULES IN AN ESKIMO CHILD WITH ACTIVE LIMBAL AND CORNEAL PHLYCTENULES. (FIG. 3) THE VASCULARIZED SCAR RESULTING FROM A FASCICULAR ULCER. (FIG. 4) MARGINAL ULCER RESULTING FROM A CORNEAL PHLYCTENULE JUST CENTRAL TO THE LIMBUS. (FIG. 5) MILIARY CORNEAL PHLYCTENULES IN A YOUNG INDIAN BOY. (FIG. 6) DENSE CENTRAL SCARS RESULTING FROM RECURRENT PHLYCTENULOSIS.

FIG. 7

FIG. 8

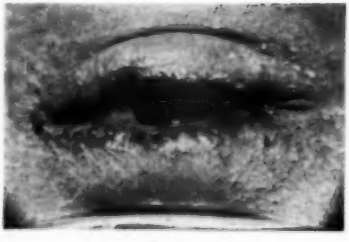

FIG. 9

FIG. 10

FIGS. 7 TO 10 (THYGESON). (FIG. 7) DRAWING OF PHLYCTENULAR PANNUS, IN A YOUNG INDIAN BOY. (FIG. 8) DRAWING OF PHLYCTENULAR PANNUS, SHOWING IRREGULAR VASCULARIZATION. (FIG. 9) RECURRENT PHLYCTENULOSIS IN AN ALASKAN INDIAN GIRL, ASSOCIATED WITH INFECTIOUS ECZEMATOID DERMATITIS OF STAPHYLOCOCCIC ETIOLOGY. (FIG. 10) RECURRENT PHLYCTENULOSIS IN AN ALASKAN INDIAN GIRL, ASSOCIATED WITH A CHRONIC DIPLOBACILLARY BLEPHARITIS.

criminated as a major cause of blindness.[9]

There is no doubt that it is a major cause of reduced vision among the Indians and Eskimos of Alaska, Canada, and Greenland, and probably among all the natives of the far north.

Reports on its incidence and severity in Alaska were first made by Fields[7] and by Fritz,[10] and their observations have been confirmed by our studies at Mt. Edgecumbe in the summers of 1949 and 1950. Table 1 analyzes the visual findings in 200 Alaskan Indian, Aleut, and Eskimo children in the Mt. Edgecumbe native school.

TABLE 1

VISUAL ACUITY IN RELATION TO PHLYCTENULOSIS

Visual acuity (uncorrected) of 101 individual eyes of Indian and Eskimo children with phlyctenulosis scars involving the pupillary area

C.F.	20/400	20/200	20/100	20/80	20/70	20/60	20/50	20/40	Above 20/40	Total	% 20/70 or less	% Above 20/40
1	1	9	5	1	22	0	15	9	38	101	38.6%	37.6%

Visual acuity (uncorrected) of 200 individual eyes of Indian and Eskimo children with active and inactive phlyctenulosis

C.F.	20/400	20/200	20/100	20/80	20/70	20/60	20/50	20/40	Above 20/40	Total	% 20/70 or less	% Above 20/40
2	7	12	6	3	24	1	14	14	117	200	27.0%	58.5%

Visual acuity (uncorrected) of 200 individual eyes of Indian and Eskimo children without evidence of past or present phlyctenulosis

C.F.	20/400	20/200	20/100	20/80	20/70	20/60	20/50	20/40	Above 20/40	Total	% 20/70 or less	% Above 20/40
0	0	2	9	0	5	1	8	14	161	200	8.0%	80.5%

CLINICAL MANIFESTATIONS OF PHYCTENULAR OPHTHALMIA

In my experience, the various forms of phlyctenulosis have had very much the same clinical appearance wherever they have been observed, whether among Negroes, Indians, Eskimos, or whites. In the native children studied at the Mt. Edgecumbe school, all forms of the disease, except that associated with perforating marginal ulceration, were to be seen.

This exceptional form does occur in the natives of Alaska, however; in the tuberculosis sanatorium at Mt. Edgecumbe, there were two patients with phthisis bulbi who gave a history of perforating ulceration in childhood and, in the school, one child was seen with adherent leukoma which apparently had resulted from perforation of a marginal phlyctenule.

The following descriptions of the clinical forms of phlyctenulosis are based, therefore, on observations of cases seen in the course of our Alaskan surveys of 1949 and 1950, and on observations of recent cases seen in private practice and in the clinic of the University of California Medical School.

1. *Phlyctenulosis as a conjunctivitis without keratitis.* This form is characterized by the occurrence of one or more phlyctenules located selectively at the limbus (fig. 1) although occasionally they may be scattered over the bulbar conjunctiva or even over the palpebral conjunctiva (fig. 2). The individual phlyctenules vary in size from just visible points to nodules several millimeters in diameter. Each lesion, except some of the smallest ones, may be seen to follow a regular course of evolution from infiltration to ulceration to resolution, the entire process taking from 10 to 12 days. In any one attack,

phlyctenules in the various stages of evolution can usually be seen.

Associated with the phlyctenules there is usually a diffuse conjunctival hyperemia and mild cellular infiltration with scanty conjunctival discharge. The cytology of the exudate is nonspecific and I never have seen a case with conjunctival eosinophilia. Epithelial keratitis, so common a feature of many types of conjunctivitis, has not been a constant nor characteristic feature of phlyctenulosis and when present usually suggests a secondary staphylococcic infection.

The individual attacks are usually self-limited but may occasionally persist for many weeks and, in this event, almost always progress to corneal involvement. In the strictly conjunctival cases the subjective symptoms are mild. This is in marked contrast to the extraordinarily severe photophobia which is characteristic of the cases in which there is also corneal involvement.

Involvement of the palpebral conjunctiva seems to be characterized by rows of phlyctenules close to the free lid border (fig. 2). In the two cases seen in Eskimo children the upper tarsal conjunctiva was much more involved than the lower. Both cases were under daily observation and the phlyctenules were seen to evolve just as they did when located at the limbus, and to heal in the same way, without cicatrization.

2. *Phlyctenulosis as a keratoconjunctivitis.* This is the most characteristic and important form of the disease and the form to which most conjunctival cases eventually progress. In fact, it is apparently only rarely that a phlyctenulosis starts as a keratoconjunctivitis and I know of no case that has started as a pure keratitis.

The diagnosis of the keratitis must in the final analysis be based on the occurrence of limbal or conjunctival phlyctenules since none of the corneal lesions can be considered truly pathognomonic. Characteristic, if not pathognomonic, corneal lesions do occur, however, and may be described as follows:

a. THE FASCICULAR ULCER OR WANDERING PHLYCTENULE. This is perhaps the most characteristic of all the corneal lesions of phlyctenulosis. It consists in the progression of a limbal phlyctenule centrally across the pupillary area; in its wake it leaves a narrow, superficial, vascularized scar (fig. 3). Several of these fascicular ulcers may occur in a single eye and visual acuity is usually reduced as a result.

b. MARGINAL ULCERS. These may be considered as abortive forms of the fascicular ulcer. They involve the cornea at the limbus and do not leave the narrow clear space between ulcer and limbus which is so characteristic of the ordinary catarrhal ulcer fig. 4). Furthermore, the long axis of the ulcer and the resulting scar are often perpendicular to the limbus instead of parallel to it as they are in the catarrhal ulcer.

Of course typical marginal ulcers also occur occasionally in phlyctenulosis; in view of the high incidence of secondary staphylococcic infection in the disease it is more than likely that some of these are actually due to the secondary infection.

c. MILIARY CORNEAL PHLYCTENULES. Rare cases are seen in which minute phlyctenules cover the corneal surface (fig. 5). I have seen only one typical example of this rare type of corneal involvement.

d. DIFFUSE CENTRAL INFILTRATES, DEEP OR SUPERFICIAL, WITHOUT ULCERATION. These are seen most commonly in phlyctenulosis of long standing which has undergone a number of recurrences. They usually lead to an ingrowth of superficial or deep vessels, depending on the depth of the lesions and their distance from the limbus. Dense central scars with minimal vascularization are occasionally to be seen (fig. 6), however, probably as a result of destructive infiltrates of short duration whose course was too rapid to permit much vessel extension.

e. PHLYCTENULAR PANNUS. The pannus of phlyctenulosis, unlike the architecturally regular pannus of trachoma, is character-

istically irregular. The vascularization is usually more prominent below than above (fig. 7), and more often incomplete than complete (fig. 8). The pannus of phlyctenulosis is apparently usually a result of diffuse, nonulcerating, central infiltrates.

From the descriptions of these various corneal lesions, it is apparent that the residuals of old, healed phlyctenular keratitis, while not pathognomonic, must certainly be considered characteristic. In children the diagnosis of healed phlyctenulosis can be made with a high degree of accuracy because of the absence usually of confusing clinical pictures such as those produced by acne rosacea keratitis, recurrent staphylococcic marginal ulcers, recurrent herpes corneae, and so forth.

3. *Phlyctenulosis as a conjunctivitis or keratoconjunctivitis with eczema of the lids.*

In view of Fuchs's use of the term "conjunctivitis eczematosa" and the tendency of early workers with the disease to consider eczema and phlyctenulosis as having a common etiology, this form of the disease would seem to be particularly important. I have the impression, however, that it is much less common than it was formerly.

Moreover, the meaning of the term "eczema" has changed in the course of dermatologic progress and the eczema of 50 years ago has now been subdivided into a number of clinical and etiologic entities, including atopic dermatitis, dermatitis venenata, seborrheic eczema, infectious eczematoid dermatitis, and so forth.

I never have seen an atopic dermatitis, now synonymous with clinical eczema, in association with phlyctenular keratitis, but I have seen a considerable number of cases with an associated severe infectious eczematoid dermatitis of staphylococcic origin (fig. 9), and a few cases with the typical macerating dermatitis of diplobacillary blepharitis (fig. 10).

Less commonly associated with the disease is the seborrheic eczema or dermatitis of seborrheic blepharitis. I have been forced to the conclusion that eczema in none of its forms is essential to the production of severe phlyctenulosis although it may play a role in stimulating and prolonging attacks, just as a febrile disease or fever therapy may induce a crop of herpes simplex "fever blisters" without being in any way etiologic.

4. *Atypical phlyctenulosis.* Phlyctenulosis offers no problem in diagnosis in its active stage when there are typical limbal phlyctenules. It is not uncommon, moreover, for the phlyctenules to appear during the course of well-defined bacterial types of conjunctival inflammation, particularly Koch-Weeks and pneumococcic conjunctivitis. In such cases the primary bacterial conjunctivitis has apparently activated a latent phlyctenulosis.

Apart from these typical cases, however, I am convinced that atypical attacks of the disease occur in which no bacterial agents are ever demonstrable and in which the phlyctenule is either absent or so insignificant as to be masked by the surrounding conjunctival infiltration.

The following case history is illustrative:

E. B., a Negress, aged 47 years, showed a bilateral diffuse conjunctivitis of both eyes with two marginal infiltrates of the left cornea. There was some thickening of the limbus opposite the infiltrates but no typical phlyctenules.

A 30-percent sodium sulfacetimide collyrium was administered and the conjunctivitis and keratitis cleared in about two weeks. It recurred four months later, however, and this time the right cornea had a single marginal infiltrate associated with three typical phlyctenules; the left eye had a catarrhal conjunctivitis with diffuse bulbar hyperemia without corneal infiltrates. This attack also lasted about two weeks.

Subsequent questioning revealed that, since childhood, this woman had had recurrent attacks of ocular inflammation highly suggestive of phlyctenulosis and that she had had a period of active pulmonary tuberculosis as a young adult.

Slitlamp study of her corneas showed several areas of typical corneolimbal scarring. Bacteriologic studies made during both attacks revealed only a normal conjunctival flora. It was concluded that the attacks in both eyes were phlyctenular in origin.

Over the years, I have seen enough similar cases of recurrent conjunctival and cor-

neal inflammation, in which bacterial agents were never demonstrable and phlyctenules rarely or never, but in which one or more of the corneal changes characteristically associated with phlyctenulosis have occurred, to conclude that many undiagnosed cases of superficial keratitis associated with superficial vascularization, infiltrates, and scars are in reality cases of phlyctenulosis, and that careful history-taking and slitlamp examination would substantiate this diagnosis. Most of these cases are in adults and most give a history of repeated attacks since childhood.

There seems to be a parallel between this situation and the so-called "keratitis metaherpetica" in which the scars of the original pathognomonic dendritic ulcer have been obliterated or disturbed by recurrent nonspecific inflammation.

Differential diagnosis of phlyctenular ophthalmia

The diagnosis of phlyctenulosis in childhood, whether active or inactive, presents no problem. In adults, however, diagnostic difficulties are introduced by such entities as acne rosacea keratitis, trachoma, recurrent staphylococcic marginal ulceration with pannus, limbal vernal catarrh, nodular episcleritis, and so forth.

The most likely of these to be confused with phlyctenulosis are acne rosacea keratitis and recurrent staphylococcic marginal ulcerations with pannus.

Were it not that the diagnosis of rosacea keratitis depends on the simultaneous presence of a facial rosacea, the differential diagnosis between it and phlyctenular keratitis would be difficult indeed, since rosacea often has limbal excrescences difficult to distinguish from phlyctenules and the infiltrates of rosacea, both marginal and central, with the accompanying pannus, all bear a resemblance to the comparable lesions of phlyctenulosis. It is fortunate that the fascicular ulcer, so characteristic of phyctenulosis, is not a feature of rosacea keratitis, and it should be remembered that the dilated conjunctival vessels of rosacea are a valuable diagnostic aid.

In recurrent staphylococcic marginal ulceration, the pannus which often develops can be confused with phlyctenular pannus, but careful analysis of the corneal picture usually resolves the diagnostic problem. Staphylococcic keratitis never shows fascicular ulceration and lacks the marginal scarring extending to the limbus which is so characteristic of phlyctenular keratitis. Scars in the pupillary area, which are very common in phlyctenulosis, almost never develop in staphylococcic keratitis.

Trachoma is usually not difficult to differentiate from phlyctenulosis because of the characteristic architecture of trachoma pannus, with its greater extension in the upper corneal quadrants. While working among the Apache Indian children, however, I was struck by the frequency with which phlyctenulosis and trachoma occurred in the same child, with the simultaneous presence of phlyctenules, fascicular ulcers, limbal follicles, pannus ulcers, trachoma pustules, and so forth. In only one of the Alaskan children with phlyctenulosis was there a pannus resembling the pannus of trachoma. This child did not have trachoma and the other eye showed the changes typical of phlyctenulosis.

Vernal catarrh and nodular episcleritis have occasionally been mistaken in their early stages for phlyctenulosis by virtue of the focal limbal infiltrations they sometimes develop. As the diseases evolve, however, the diagnosis soon becomes clear.

Etiology

No specific bacterium has ever been recovered from phlyctenular ophthalmia. The characteristic lesion of the disease, the phlyctenule, is not a specific pathologic entity comparable to the tubercle. It is essentially a focal, subepithelial, leukocytic infiltration, with small round cells predominantly, and has been likened to a subepithelial abscess by reason of its evolution to ulceration, evacua-

tion, and healing. It is now generally recognized as a manifestation of bacterial allergy bearing a resemblance to the well-known bacterids of the skin.

Unfortunately the various bacterids do not differ pathologically; for example, in the skin the trichophytid appears to be identical histologically with the tuberculid. There has certainly been no evidence advanced to indicate that the phlyctenule is a specific

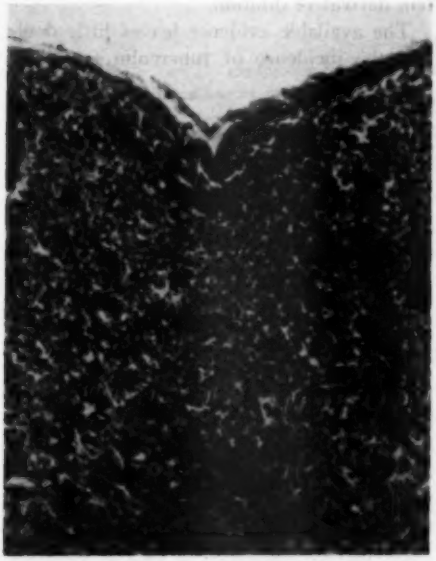

Fig. 11 (Thygeson). Low-power view of section of a phlyctenule from an Eskimo child, showing subepithelial infiltration with small round cells. (Hematoxylin-eosin.)

tuberculous lesion. Even the concept that it is necessarily an evidence of bacterial allergy has been questioned and claims have even been made for the experimental production of phlyctenules by ordinary proteins such as horse serum and pollens.

Pathologic examination of material from phlyctenulosis cannot, therefore, be expected to yield etiologic evidence, but the resemblance of the phlyctenule to the bacterids of the skin leaves little doubt as to the essential bacterio-allergic nature of the lesion. Figures 11 and 12 illustrate a bulbar phlyctenule excised from an Eskimo child. As can be seen, the lesion is essentially a focal subepithelial infiltration with small round

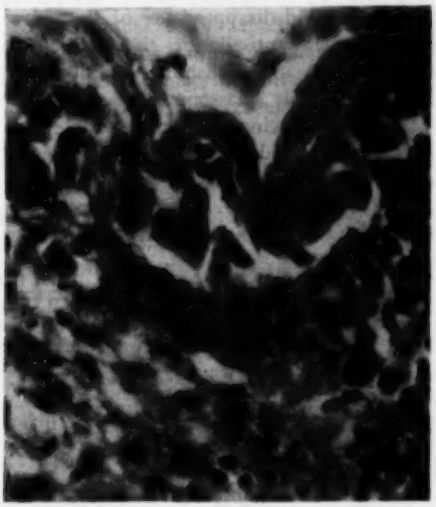

Fig. 12 (Thygeson). High-power view of section shown in Figure 11.

cells and with no specific cell arrangements or characteristics such as are to be found in lymphoid follicles.

The theory that phlyctenulosis is an allergy to bacterial proteins of the tubercle bacillus is based on the following findings in patients with the disease:

1. The high incidence of positive tuberculin reactions.

2. The high incidence of radiographically demonstrable tuberculous chest lesions.

3. The high incidence of a history of past or present tuberculosis.

4. The high incidence of family history of tuberculosis.

5. The high incidence of subsequent clinical tuberculosis.

6. The clinical similarity of phlyctenular ophthalmia to the complications of the ophthalmo-reaction of Calmette in tuberculous patients.

7. The significant incidence of previous

phlyctenulosis in adults suffering from tuberculosis.

8. The worldwide parallelism between the incidence of tuberculosis and the incidence of phlyctenulosis.

9. The rapid disappearance of the phlyctenule under anti-allergic therapy known to be capable of abolishing the tuberculin reaction, notably cortisone therapy.

In the following paragraphs these factors are analyzed in the light of personal experience and a review of the literature.

1. *The tuberculin reaction in phlyctenular ophthalmia.* The extraordinarily high incidence of positive reactors in phlyctenulosis patients has been noted by the majority of observers since the introduction of the tuberculin test. In England, for example, Sorsby[11] tested 592 cases of phlyctenular ophthalmia in children and found a tuberculin-positive incidence of 84.8 percent as against 15.3 percent in 900 cases of blepharitis. He noted that the incidence of positive reactors was almost identical in groups of young and of old patients, a noteworthy finding which would seem to indicate early infection with tuberculosis in phlyctenulosis patients.

In my experience a positive tuberculin reaction has been an almost constant finding in phlyctenulosis. In a few exceptional cases, particularly in the white population, the test has been consistently negative but, for the most part, the degree of sensitivity has been high and only rarely has it been necessary to employ the lower dilutions of old tuberculin or purified protein derivative.

Table 2 gives the findings in 295 Eskimo and Indian school children. As can be seen, the incidence of positive reactors in the phlyctenulosis-negative group was very high (86.1 percent), but the children with phlyctenulosis, both active and inactive, were uniformly positive. It must be remembered that the mortality from tuberculosis among the natives has been said to be the highest in the world. In only two among the 105 inactive phlycentulosis cases was it necessary to employ the second strength purified protein derivative dilution.

The available evidence leaves little doubt that the incidence of tuberculin sensitivity is significantly higher among phlyctenulosis patients than it is in the general population.

TABLE 2

TUBERCULIN TESTS IN ESKIMO AND INDIAN SCHOOL CHILDREN IN RELATION TO INCIDENCE OF PHYLCTENULOSIS

(Mt. Edgecumbe, 1949)	Total No. of Cases	Tuberculin Positive	Tuberculin Negative	Tuberculin Positive
Active phlyctenulosis	10	10	0	100%
Inactive phlyctenulosis	105	105	0	100%
No evidence of past or present phlyctenulosis	180	155	25	86.1%

2. *Radiographic evidence of pulmonary tuberculosis.* It is well known that phlyctenulosis, like tuberculous uveitis, is not typically a disease of tuberculous sanitaria. Nevertheless, the majority of reports in the literature stress the high incidence of radiologic evidence of primary tuberculosis in children with phlyctenulosis.

In Sorsby's[11] analysis of 510 cases he found 368, or 72.2 percent, with radiographic evidence of tuberculosis and only 60, or 11.7 percent, definitely negative. In his control series of 87 children with blepharitis, only 14, or 16.1 percent, had positive radiologic findings while 50, or 57.5 percent, were definitely negative. Burgin and Higgins,[12] in 1938, reported on a series of 502 cases of phlyctenulosis in which they found radiologic or clinical evidence of tuberculosis in 109 cases, in only three of which the patients were critically ill. The remainder

had had "primary" or childhood tuberculosis.

No routine X-ray studies were made of the cases I saw in New York and Arizona but, in our Alaskan series, routine radiologic studies were made in all cases of active and inactive phlyctenulosis among the school children. There was no difficulty in demonstrating radiologic evidence of primary tuberculosis in all cases. Unfortunately time did not permit a control series but it is hoped one can be run in the course of future studies.

3. *History of past or present clinical tuberculosis.* Divergent views as to the incidence of clinical tuberculosis in phlyctenular ophthalmia are to be found in the literature. There is no doubt of the high incidence of tuberculous infection as evidenced by positive X-ray findings, but the incidence of active pulmonary disease has varied greatly in the different series.

Analysis of these is complicated by the failure of many observers to differentiate clinical tuberculosis from subclinical tuberculosis.

Sorsby's[11] series is of special interest. Among 592 children with phlyctenular ophthalmia, 38 or 6.4 percent had clinical tuberculosis; of these, 26 showed active pulmonary disease and 12 showed extrapulmonary disease of the cervical glands, bones, and meninges. There were no cases of clinical tuberculosis in 900 cases of blepharitis.

My own experience has resembled Sorsby's. There has been a small but definite incidence of active tuberculosis in our various series of phlyctenulosis cases, particularly among the Negro children of Harlem. The Alaskan studies of this aspect of the problem were interesting but inconclusive. Table 3 shows the incidence of active and inactive phlyctenulosis in three groups at Mt. Edgecumbe.

The first group, composed of school children, showed no clinically active tuberculosis at the time of the examination but a small number had previously been patients in the orthopedic hospital because of bone and joint tuberculosis, or in the tuberculosis sanatorium because of pulmonary disease.

TABLE 3

INCIDENCE OF PHLYCTENULOSIS IN ALASKAN NATIVES

(Mt. Edgecumbe, 1949)	School Children	Children in Orthopedic Hospital	Patients in Tuberculosis Sanatorium
Active phlyctenulosis	10	1	2
Inactive phlyctenulosis	133	29	55
No evidence of past or present phlyctenulosis	261	36	109
Total no. of cases	404	66	146
Phlyctenulosis index	35.4%	45.4%	25.3%

The second group was composed of children with active bone and joint tuberculosis but no pulmonary activity; 30 of the 66 had had phlyctenulosis. Only one of these was active at the time of examination but the surgeon in charge informed us that there was always at least one active case and that there were often several. There was no record of the number of active cases in any one year but it can be presumed to have been significantly high.

The third group, composed of native patients of all ages at the tuberculosis sanatorium, showed a lower incidence of inactive phlyctenulosis than the orthopedic hospital children but there were two active cases. Physicians in charge of the sanatorium in-

formed us that here were almost always one or two cases of active phlyctenulosis but that no record of the incidence had been kept.

4. *Family history of tuberculosis.* There seems to be general agreement in the literature that the incidence of family history of tuberculosis is higher in groups of phlyctenulosis cases than in control groups. For example, Weekers[13] reported a family history of tuberculosis in 88 of 156 cases; Blair[14] in 20 percent of 305 cases; Burgin and Higgins[12] in 22 percent of 502 cases; Stephenson and Jamieson,[15] in 15 of 20 cases; and Cohen,[16] in 63 of 123 cases (adults only).

Friedenwald and Robertson in an unpublished study found that 20 cases out of 21 had been exposed to open tuberculosis in their families or immediate contacts. Sorsby[11] investigated the family history of tuberculosis in 263 cases and found an incidence of 76 or 28.9 percent. He compared this with an incidence of 3.7 percent in the normal school population as computed by Bently in 1931.

In my own experience, I have been impressed by the high incidence of familial tuberculosis in phlyctenulosis cases. This has been equally true in all groups, whether white, Negro, Indian, or Eskimo. I have inquired routinely into the family history of every case seen in practice and agree with the conclusion that phlyctenulosis in a child is usually an indication that an active case of tuberculosis is present in his environment. In Alaska we were unable to obtain accurate information on this point but the incidence of tuberculosis in the family was obviously very high.

5. *Incidence of subsequent clinical tuberculosis.* In 1938, Ajo[17] reported the results of an after-history survey of 449 cases of phlyctenulosis seen in Helinski during the years 1912 to 1927. Satisfactory follow-up information was obtained in 367 patients, of whom 55, or 15 percent, had died at an average period of 7.4 years after the onset of the phlyctenulosis, death having been due to tuberculosis in 35, or 9.5 percent. The mortality from tuberculosis in this group was about twice as high as the mortality from tuberculosis in the general population.

It was possible to make a clinical examination of 89 of these patients, and adequate hospital records were available for an additional 11. Thirty-nine of the 100 cases showed evidence of tuberculosis—pulmonary in seven cases, of the cervical glands in nine, and of various other tissues in the remaining 23. Ajo[17] concluded that phlyctenulosis carried an unfavorable prognosis with respect to the development of later clinical tuberculosis.

Other reports include those of Igersheimer and Prinz[18] (1922), Nassau and Zweig[19] (1925), Carvill[20] (1929), and Woringer,[21] as illustrated in Table 4. All concluded that phlyctenulosis was associated with a high subsequent development of active clinical tuberculosis.

Sorsby[11] reported on the after-history of 754 cases of phlyctenular ophthalmia as compared with 526 cases of blepharitis and 498 cases of conjunctivitis, all treated at White Oak Hospital in London from 1921 to 1931. His information was obtained by reviewing the records of reported cases of tuberculosis for the area served by this hospital. He found an incidence of 5.3 percent in the phlyctenulosis group as compared with 0.95 percent in the blepharitis group and 0.6 percent in the conjunctivitis group. The mortality rate from tuberculosis in the phlyctenulosis group was about seven times as high as in the control groups.

I have had no experience with this aspect of the problem but it is to be hoped that after-history data will accumulate from the Alaskan studies now in progress.

6. *The experimental production of phlyctenules by the ophthalmo-reaction of Calmette and other methods.* According to Sorsby,[11] the test introduced by Calmette and Wolff-Eisner in 1907, and later abandoned because of the severity of the corneal reaction, can produce in tuberculous patients a

severe conjunctivitis and keratitis clinically similar to phlyctenular ophthalmia.

Even the subcutaneous use of tuberculin in large doses, according to the procedure originally used in the treatment of tuberculosis, has apparently precipitated attacks of phlyctenulosis, and a few observers, including Igersheimer and Prinz,[18] have noted the appearance of phlyctenules after treatment with tuberculin.

In 1910, Weekers[13] and Rosenhauch,[22] working independently and following different experimental methods, produced phlyctenulosis in rabbits previously sensitized by infection with bovine tubercle bacilli.

Weekers[23] instilled tuberculin into the conjunctival sac, as in the Calmette tuberculin test, and obtained phlyctenules which were clinically and histologically comparable to those which develop in human cases. His results have been confirmed by numerous workers, including Kuboki[24] (1924), Kuniya[25] (1935), and others.

Rosenhauch,[22] and later Rubert,[26] Funaishi,[27] Polev and Sawalsky-Fissan,[28] and Kuniya,[25] obtained similar results from the instillation of either living or dead Staphylococcus aureus organisms. This method appeared to be effective less regularly than the tuberculin method but it has theoretical importance which will be discussed later in connection with the high incidence of staphylococcic infection in phlyctenulosis cases.

7. The incidence of previous phlyctenulosis in adults suffering from tuberculosis. As mentioned earlier, phlyctenulosis has not seemed to be, in this country at least, a problem of great importance in sanatoriums for the treatment of adults with pulmonary tuberculosis. Reports in the literature on the frequency of old, healed phlyctenulosis in adults with active tuberculosis vary, moreover.

Thus Nowak[29] (1922) found that 15 (38 percent) of 39 adults with tuberculosis showed evidence of previous phlyctenular ophthalmia, whereas Igersheimer and Prinz[18] (1921) reported the incidence of previous phlyctenulosis in a series of 2,144 cases as only 47 (2.2 percent).

I have no data which could serve to clarify this point but I have been impressed by the paucity of active phlyctenulosis and of tuberculous uveitis in the sanatoriums I have visited. In my practice, on the other hand, I have at present three patients who have been under recent sanatorium care who are suffering from recurrent phlyctenulosis. In all three cases, the phlyctenules have been bulbar rather than limbal and there has been no corneal activity although two of the cases show corneal scars from old phlyctenulosis.

TABLE 4

SEX INCIDENCE OF PHLYCTENULOSIS IN ESKIMO AND INDIAN SCHOOL CHILDREN

	1949—Mt. Edgecumbe		1950—Mt. Edgecumbe and Sheldon-Jackson	
	Males	Females	Males	Females
Active phlyctenulosis	2	8	3	1
Inactive phlyctenulosis	62	71	79	65
No evidence of past or present phlyctenulosis	142	119	276	222
Total no. of cases	206	198	358	288
Phlyctenulosis index	31.0%	39.9%	22.9%	23.1%

In our survey of the tuberculosis sanatorium at Mt. Edgecumbe, in which both children and adults were cared for, the incidence of corneal scars due to phlyctenulosis was 25.3 percent in 146 cases in 1949, and 38.8 percent of 116 patients in 1950. Unfortunately these figures do not differentiate between adults and children.

On the other hand, in the orthopedic hospital, in which only children with bone and joint tuberculosis are cared for, this incidence was 45.4 percent of 66 patients in 1949, and 42.8 percent of 63 patients in 1950.

8. *The worldwide parallelism between incidence of tuberculosis and incidence of phlyctenulosis.* A review of the literature clearly indicates a relationship between the incidence of tuberculosis and the incidence of phlyctenulosis. In the United States and Alaska the phlyctenulosis problem is most important in just the population groups in which tuberculosis is most rampant—that is, in the Indians, Aleuts, and Eskimos of Alaska, and the Negroes and Indians of the United States.

In our Alaska studies of 1950 Fritz and I[30] studied two villages of southeastern Alaska, one (Angoon) with a high incidence of active pulmonary tuberculosis (17.7 percent) and the other (Hydaburg) with a low incidence (3.0 percent), and found the phlyctenulosis index to be 27.3 percent in Angoon and 10.6 percent in Hydaburg.

According to Dr. Jack C. Haldeman, medical officer in charge of the Arctic Health Research Center, tuberculosis was reported as the cause of death on 43 percent of all death certificates for Indians, Eskimos, and Aleuts in Alaska in 1946, which was 10 times as often as in the United States as a whole. Although there are no figures on the incidence of phlyctenulosis in the United States as a whole, it can certainly be assumed, on the basis of the observations made in the course of this study, that it is less than one tenth as great as it is among the natives of Alaska.

9. *Rapid disappearance of the phlyctenule under anti-allergic therapy, notably cortisone therapy.* Cortisone, a hormone of the adrenal cortex, introduced for the treatment of rheumatoid arthritis, has been most useful in the treatment of diseases in which allergy, and particularly bacterial allergy, is a prominent factor; conversely, it has had little effect in diseases in which allergy is of little or no importance, such as poliomyelitis.

The ability of cortisone to abolish the tuberculin skin reaction has been well demonstrated, and Fritz and I[31] were able to show that subconjunctival or topical administration of the drug would abort acute phlyctenulosis typically in from 24 to 48 hours. This result certainly supports the theory that the phlyctenule is an allergic manifestation.

Other observations having a possible bearing on etiology

Age distribution. All observers are in agreement that phlyctenulosis is essentially a disease of children and young adults although it may develop for the first time, usually in a mild form, in adults of advanced age. There is no agreement in the literature as to whether the greatest number of cases occur in the first or in the second decades.

Krasso[32] has claimed that there are two peak periods, one at from three to four years of age and the other at 15 years of age. This is supported by the data of Rolett[33] and Frominopoulos[34] but not by the series reported by Guttmann[35] and Grönholm[36] in which there were no peak ages.

My own experience has certainly confirmed the view that phlyctenulosis is essentially a disease of childhood. The earliest age at which I have seen an active case is four months. This was a white child in California who had been exposed to open tuberculosis in his mother. Most of those seen in private practice have been in the 8-to-15-year age group, but it should be borne in mind that the first attacks in childhood are often either left untreated or are

seen only by pediatricians or general practitioners.

In our Alaskan series of active and inactive cases the youngest patient was a child, aged four years, and the oldest a young adult, aged 27 years, with the peak at age 16 years. Considering the 10 active cases only, we see an even distribution between the two age groups—9 to 11 and 15 to 19 years.

Each child was questioned for a history of previous attacks of inflamed eyes. A reliable differentiation between a banal conjunctivitis and phlyctenulosis could not be made although some of the older children described accurately the spotty bulbar inflammation of phyctenulosis. The general impression gained was that phlyctenulosis, at least among the Alaskan natives, starts in the preschool years.

TABLE 5

INCIDENCE OF BLEPHARITIS IN 100 CASES OF ACTIVE AND INACTIVE PHLYCTENULOSIS

(Mt. Edgecumbe, 1949)	Total No. of Cases	No. of Cases with Blepharitis	Cases with Blepharitis
Active phlyctenulosis	10	4	40%
Inactive phlyctenulosis	90	37	41%

Sex distribution. With only a few exceptions, all writers on phlyctenulosis are in agreement that the disease is much more common in the female than in the male.

Guttmann[28] noted that the difference in sex incidence became apparent at about the fifth year of life and increased with age. Sorsby[11] reported on 1,392 children with phlyctenulosis admitted to the White Oak Hospital in London between the years 1925 and 1940; 60.9 percent were girls and 39.1 percent were boys. In a control series of 2,646 other children admitted for blepharitis and chronic conjunctivitis, 46.3 percent were girls and 53.7 percent boys.

In our 1949 Alaskan series of active and inactive cases (Table 4), there was a decided sex difference in favor of the female, and only two of the 10 active cases were males; in the same study there were more males (136) than females (120) among the unaffected children. In the 1950 study, however, these differences did not obtain.

TABLE 6

INCIDENCE OF BLEPHARITIS IN PHLYCTENULOSIS-POSITIVE AND PHLYCTENULOSIS-NEGATIVE CASES

(Mt. Edgecumbe and Sheldon-Jackson)	Active or Inactive Phlyctenulosis	No Evidence of Past or Present Phlyctenulosis
Blepharitis	27	6
No blepharitis	121	488
Total no. of cases	148	494
Blepharitis index	18.0%	1.0%

Incidence of marginal blepharitis and lid eczema. As previously mentioned, the term "eczematous keratitis" was at one time synonymous with phlyctenular keratitis because of the high incidence of eczema of the lids which was noted by early observers of the disease.

It would appear that the incidence of this complication has been steadily decreasing along with the generally decreasing incidence of the disease itself in most parts of the world. Many of the more recent reports fail to mention lid eczema and Sorsby[11] did not consider it worth analyzing.

Neverthless, marginal blepharitis and eczema of the eyelids do occur in many cases; when working in the Vanderbilt Clinic, New York City, for example, I found an incidence of blepharitis of approximately 50 percent in cases of phlyctenulosis among the Negro children of Harlem. There was less of this complication among the Apache Indian children of Arizona but, in the 1949 Alaskan study (table 5), about 40 percent of both active and inactive cases also had blepharitis.

In most cases it appeared to be staphylococcic but there were also cases of mixed staphylococcic and diplobacillary infection.

TABLE 7

FLORA OF CONJUNCTIVA AND LID MARGINS IN NINE CASES OF ACTIVE PHLYCTENULOSIS (1949)

Case No.	Right Eye		Left Eye	
	Activity	Flora	Activity	Flora
1	+	Normal flora	+	Coagulase-positive staph.; diplobacilli
3	0	Coagulase-positive staph.	+	Coagulase-positive staph.
11	+	Coagulase-positive staph.	+	Normal flora
17	0	Alpha hem. strep.	+	Normal flora
31	0	Normal flora	+	Coagulase-positive staph.
41	+	Coagulase-positive staph.	0	Coagulase-positive staph.
52	+	Coagulase-positive staph.	0	Normal flora
97	+	Coagulase-positive staph.	+	Coagulase-positive staph.
105	+	Coagulase-positive staph.	0	Coagulase-positive staph.

In the 1950 Alaskan study (table 6), the incidence of blepharitis was much reduced in both the phlyctenulosis and the control series but was still 18 percent in the phlyctenulosis cases.

Bacterial flora of active and inactive phlyctenular ophthalmia. The early workers in phlyctenulosis were all impressed by the frequency of staphylococcic infection in the disease.

Axenfeld[37] in his *Bacteriology of the Eye,* published in 1907, summarized the literature on the bacterial flora in phlyctenulosis and concluded that staphylococci, although frequent and abundant on the phlyctenulosis conjunctiva, were not to be found constantly. He referred to his own studies in which he had failed to find the organism regularly in early phlyctenules and concluded that the incidence of positive findings was not high enough to be etiologically significant. Later workers have only amplified and confirmed these findings.

TABLE 8

BACTERIAL FLORA OF CONJUNCTIVA AND LID MARGINS IN 98 CASES OF INACTIVE PHLYCTENULOSIS (1949)

		No. of Cases	Percent Cases
Normal flora		49	50
Coagulase-positive staphylococci		40	40.8
Other pathogens:			
Nonhemolytic streptococci	1		
Alpha hemolytic streptococci	3		
Pneumococci	8		
Diplobacilli (Morax-Axenfeld)	2		
H. influenzae	3		
	17*		
Total with pathogenic bacteria		49	50

* 8 of the 17 also had coagulase-positive staphylococci and are therefore included in the 40 coagulase-positive staphylococci cases listed above.

In a Harlem series of 30 Puerto Rican and Negro children with phlyctenulosis, I was able to demonstrate coagulase-positive staphylococci in 16, or 53.3 percent. Table 7 gives the bacterial flora in nine cases of active phlyctenulosis in Alaskan native children. It will be seen (table 8) that coagulase-positive staphylococci were found in 12 of 18 eyes, or 66.7 percent; in 98 cases of inactive phlyctenulosis, coagulase-positive staphylococci were found in 40, or 40.8 percent.

Tuberculin-negative phlyctenulosis. The tuberculin test is generally considered a reliable guide to previous tuberculous infection. The test itself is not entirely reliable, however, and both false negatives and false positives have been reported. There have probably been more false negatives than false positives but the deterioration of old tuberculin in dilute solution, which has led to false negative reactions in the past, is largely avoided when purified protein derivative is used.

Nevertheless, phlyctenulosis has been known to occur in patients with negative tuberculin reactions and with no radiographic or clinical evidence of tuberculosis. In these cases it would seem logical to con-

sider as possible etiologic factors any microbic agents which tend to produce a prominent allergy-of-infection.

Nutritional deficiency. All observers of the disease have agreed that phlyctenulosis is most frequent in children from the lower economic strata of society whose diet is most apt to be deficient. There is no agreement, however, that any specific vitamin or fraction of the diet is at fault, although the possibility that riboflavin and vitamin-A deficiencies could be causal has been considered.

Other workers have suggested that an excess of carbohydrate in the diet might be related to etiology, and Cremer[38] (1929) and Lazarescu and Damian[39] (1936) suggested a deficiency in calcium as a possible etiologic factor. It is noteworthy that Sorsby[11] noted no significant deficiencies in nutrition between children with phlyctenular ophthalmia and children with blepharitis alone.

The United States Public Health Service has collected significant data on the nutrition of the Alaskan natives which we hope to be able to correlate with our phlyctenulosis studies in the future.

Therapy

In 1905, N. Bishop Harmon,[40] in his textbook *The Conjunctiva in Health and Disease*, described the treatment of phlyctenulosis as follows:

"The care of the general bodily health and the removal of all possible sources of irritation, stomatitis, decayed teeth, sores on the face, lips, and nose or nasal discharge, with the ever-president pediculi, are the first care. Cod-liver oil, or plenty of fat food, bacon, butter, etc., are invaluable in reducing the liability to further attacks. . . . In the stages of acute irritation and photophobia, probably the best application is atropine ointment, applied by the surgeon himself between the lids. Later on a slightly stimulating preparation is useful. I have found insufflations of calomel invaluable, but this is no good for home use. . . . An ointment of finely precipitated and reprecipitated yellow oxide of mercury in lanoline and vaseline of 1% and later 2% strength is good. . . . With a single phlyctenule in an early, unbroken stage the attack may be quickly absorbed by touching the pimple lightly with a fine brush dipped in a 1% solution of silver nitrate."

Until the recent introduction of cortisone, therapy seemed hardly to have progressed since 1905, and certainly no specific treatment can yet be said to exist. If one accepts the theory that phlyctenulosis is in most instances a bacterial allergy to products of the tubercle bacillus, it would seem logical to attack the disease by attacking the tubercle bacillus by chemotherapeutic means.

Up to the present time, no series of phlyctenulosis cases has been reported in which streptomycin, promizole, or para-aminosalicylic acid, the most commonly used antituberculous agents, have been employed. The underlying tuberculosis, however, has been treated indirectly by desensitization with tuberculin and by dietary measures.

Tuberculin therapy. Tuberculin desensitization ought to be valuable if phlyctenulosis is indeed due to a hyperallergic phase of tuberculosis. Favorable results have been reported by a number of workers but controlled studies of the effect of tuberculin injections is notoriously unpredictable.

Sulzberger, in his *Dermatologic Allergy*, states that administration of tuberculin can, in many instances, either increase or decrease the level of the skin's tuberculin sensitivity. Lower degrees of skin sensitivity can sometimes be raised rapidly by one or two intracutaneous injections of tuberculin.

Sulzberger[41] states further that the degree of tuberculin sensitivity can often be specifically decreased, one or a few intracutaneous injections sometimes sufficing to achieve a general, marked hyposensitization of the skin; that in many other cases the level of the skin's tuberculin sensitivity cannot be demonstrably altered by specific injections.

The relationship between the conjunctival and skin sensitivities to tuberculin has not been thoroughly explored but it is generally believed that they run in parallel.

In spite of the theoretical reasons which would favor the use of tuberculin therapy, this method has not come into general use.

Dietary therapy. If attacks of phlyctenulosis are associated with an activation of the primary tuberculous lesion, as the elevated sedimentation rates in active phlyctenulosis would seem to indicate, dietary therapy of phlyctenulosis, for its effect on the focus, would seem to be indicated. There is ample evidence that dietary therapy is of value but no agreement as to its mode of action or the relative merits of different dietary fractions.

I am in agreement with Sorsby that there is no valid evidence as yet that would incriminate nutritional deficiencies as a direct causal factor, but there is small doubt of their nonspecific effect in relation to the activity of a tuberculous focus. On many occasions in New York, I saw attacks of phlyctenulosis cease when the child was hospitalized and placed on an adequate diet, only to recur when the child returned to its home environment.

The dramatic effect of adequate diet was observed during the course of studies at the school run for trachomatous Apache children at Fort Apache, Arizona. At the time of my first visit to the school I was struck by the high incidence of active phlyctenulosis existing coincidentally with the trachoma in these children. The next year phlyctenules were only rarely seen.

Their disappearance was coincidental with the introduction of a new dietary regime for the school in which the children received for the first time adequate amounts of dairy products, fresh fruits, and vegetables.

Antiseptic therapy. A third method of therapeutic attack on phlyctenulosis has been through topical antiseptics. If secondary bacterial infections act as precipitating agents in phlyctenulosis, their control would seem to be most important. The favorable effects of the time-honored calomel treatment can only be explained on the basis of a bacteriostatic effect of the mercury liberated from the calomel.

In New York, I was impressed by the frequency with which attacks of phlyctenulosis could be aborted by prompt treatment of an associated blepharitis and I gained the impression that recurrences could often be prevented by controlling secondary infection, and staphylococcic infection in particular.

Cortisone therapy. The most recent and certainly the most promising method of attack so far developed is the topical use of cortisone. Favorable results in isolated cases have been recorded by von Sallmann, McLean and Gordon, and others. Fritz and I[31] reported a series of 18 cases in which topical instillations or subconjunctival injection resulted in rapid disappearance of the lesions, usually within 24 to 48 hours.

The effect of the cortisone appeared to be much more rapid than the effect obtained with any other method of treatment. The few recurrences after therapy was discontinued responded rapidly to a second course of the drug.

An intensive trial with cortisone is being undertaken in Alaska this winter and it is hoped that it may be the means of reducing materially the incidence of the corneal scars so prevalent among Alaskan native children.

Although cortisone can of course not be considered curative, since it can have no action on the systemic cause of the disease, its ability to abort acute attacks, and thus to prevent corneal ulceration and cicatrization, is obviously of very great value.

Discussion

An analysis of the literature and personal experience leave no doubt of the close association between tuberculosis and phlyctenular ophthalmia. The theory that the phlyctenule is, in the majority of cases, a manifestation of local conjunctival sensitization to the circulating products of the tubercle bacillus appears to fit in well with the known facts. There are a number of features that need clarification by future research, however.

Carefully controlled studies of the varia-

tions in skin and conjunctival sensitivity as related to acute attacks should be made, as well as clinical and radiographic studies of the state of the primary tuberculous focus as related to conjunctival activity.

The exact reasons why phlyctenulosis is more common in childhood than in adult life, and more common in clinically inactive than in clinically active tuberculosis, must be determined.

If phlyctenulosis is a nonspecific bacterial allergy, as all available evidence indicates, the predominance of tuberculosis in its etiology is of theoretic interest at least, and there must be some explanation for it.

Bacterial allergy is a common feature of infectious disease and is to be observed particularly in the granulomatous diseases. In certain of these, such as coccidioidomycosis, histoplasmosis, lymphogranuloma venereum, and brucellosis, skin sensitivity of a high order is commonly elicited.

Of these, only coccidioidomycosis has been shown to affect children to any degree and there is suggestive evidence to indicate that phlyctenules can be produced in this disease. The failure of the other diseases to be incriminated as causes of phlyctenulosis may be due to the relative infrequency of early childhood infection with them, since childhood seems to be the susceptible age for phlyctenulosis.

It is of theoretic interest that congenital syphilis has not been advanced as a cause of phlyctenulosis in view of the fact that allergy is not a prominent feature of this disease and that no skin-sensitivity test has proved to have any clinical value with respect to it.

A distinct parallelism seems to exist between the phlyctenule and the tuberculid of the skin. The tuberculid is considered to be an allergic response of sensitized skin to hematogenous distribution of tubercle bacilli.

According to Sulzberger, an "id" is a "secondary manifestation appearing in a specifically altered (allergic) tissue produced by microorganisms emanating from a remote focus, and/or by the allergenic products of such microorganisms. In some instances the tissue-allergy and other local conditions are such that the microorganisms are rapidly altered, eliminated, or destroyed. Under such circumstances the microorganisms are either demonstrable only with difficulty or are not to be found in the lesions."

Apparently in the tuberculid there may occasionally be a characteristic tubercle formation, but usually the histologic picture is nonspecific and comparable to the phlyctenule.

If the phlyctenule were due to showers of organisms rather than to soluble products of the tubercle bacillus, one would expect to find a high frequency of associated uveal and skin lesions.

None of our Alaskan native schoolchildren with active phlyctenulosis had uveal lesions or focal lesions of the skin, and I recall having seen only two active phlyctenulosis cases in which there were also tuberculids of the skin. Since I was not looking specifically for skin lesions at that time, it is of course possible that I may have missed some. This relationship, if any, between the phlyctenule and the tuberculid must be further explored in coöperative studies between the dermatologist and the ophthalmologist.

Phlyctenulosis appears to be common among the natives of the Canadian north as well as of Alaska. Dr. M. R. Marshall[42] of the University of Alberta surveyed, in the summers of 1947 and 1949, almost the entire native population of the settlements along the lower Mackenzie River from Fort Norman to Aklavik and found among the Indians and Eskimos a high incidence of corneal scarring due to phlyctenulosis, much of it involving the central areas. A program of treatment and prevention has been undertaken by the Canadian government.

It is of interest that in a nutritional survey of the Eskimos of Southampton Island in 1947 and 1948, Brown and co-workers[43] reported a 4.9 percent incidence of corneal opacities. Dr. Curtis,[44] medical director of the Grenfell Mission in Labrador, wrote me

that corneal scars, presumably due to phlyctenulosis, were seen commonly among the Eskimos of his territory.

The disease seems also to be common in Greenland but I was able to locate only one pertinent survey: Skeller,[45] in 1949, reported finding active or inactive phlyctenulosis in 43 percent of 679 natives with eye complaints.

Tuberculosis is the major medical problem among these peoples of the north and this, along with the poor hygiene conditions, probably explains the high incidence of phlyctenulosis.

Future research must be directed toward analyzing the tuberculin-negative cases of phlyctenulosis which, according to Sorsby's[11] series, may constitute as much as 15 percent of all cases. I feel, however, that this figure would be reduced considerably by the use of graded dilutions of tuberculin.

While it is probable that all cases of phlyctenulosis are of endogenous origin, from tuberculosis or other granulomatous disease, the possibility of rare exogenous sources must be considered.

Staphylococcus aureus is the only bacterium which has been associated with the disease with any constancy. Sulzberger,[41] in his *Dermatologic Allergy*, states that staphylococcic lesions "often represent combinations of intrinsic damaging action of staphylococcus toxins combined with allergic reactions based on sensitivity to other staphylococcic allergens."

So far I have encountered only three cases of tuberculin-negative phlyctenulosis in which staphylococcic allergy could be demonstrated, and I have seen no phlyctenules arise in the course of experiments on human volunteers in whom experimental staphylococcic conjunctivitis was produced by the instillation of staphylococcus toxin. Further exploration along these lines is clearly indicated, however.

In spite of occasional claims to the contrary, I feel certain that phlyctenulosis never results from allergy to nonbacterial proteins, such as are concerned in hay fever and urticaria. I never have seen phlyctenules develop in a simple allergic conjunctivitis or in a vernal catarrh, and I never have found in phlyctenulosis the conjunctival eosinophilia that is so constant a feature of the nonbacterial allergies. Furthermore, recent reports indicate that the antihistamines are of little if any value in the treatment of phlyctenulosis and it is well known that they are ineffective in bacterial allergy in general.

An interesting feature of phlyctenulosis is the lack of any direct relationship to uveitis. Uveitis secondary to the severe corneal changes of phlyctenulosis seems to be transient in nature since it clears rapidly with subsidence of the corneal infiltrates.

The phthisis bulbi observed in rare instances among the Alaskan natives probably follows perforating ulcers and may well be due to pyogenic bacteria rather than to the phlyctenulosis mechanism itself. In none of our Alaskan children with active or inactive phlyctenulosis did we encounter an associated uveitis.

In comparing uveitis and phlyctenulosis, one is impressed first of all by the age incidence. Unlike phlyctenulosis, uveitis is rare in childhood and, when it does occur, it is almost always granulomatous. The nongranulomatous type of uveitis, generally believed to be a bacterial allergy, is primarily an adult disease with the peak of cases probably falling in the 20-to-40 years of age group.

There are certain striking similarities between nongranulomatous uveitis and phlyctenulosis, however; for example, the fact that both are characteristically recurrent, that both are responsive to cortisone therapy, and that in both the early attacks tend to be benign and the later attacks to be associated with severe, necrotic lesions.

Perhaps the Arthus phenomenon, as suggested by Woods[46] in relation to nongranulomatous uveitis, would explain both these disease manifestations. In any event, and in spite of the differences between them, the study of phlyctenulosis, because of its

greater accessibility to clinical and pathologic study, may help to elucidate the mechanisms of bacterial allergy as displayed in uveitis.

Summary and Conclusions

1. Phlyctenular keratoconjunctivitis, while much reduced in incidence in recent years, is still a major cause of visual disability throughout the world and particularly in the native populations of the Arctic regions.

2. The incidence of phlyctenulosis throughout the world appears to parallel roughly the incidence of tuberculosis; that is, it is highest in areas in which the death rate from tuberculosis is highest, such as Alaska. In Alaska the incidence of corneal scarring due to phlyctenulosis, as judged by surveys of groups of unselected school children from all parts of the territory, is apparently 25 percent or more.

3. All available evidence seems to indicate that phlyctenulosis is in most instances an allergic manifestation of a primary tuberculous infection, occurring principally in childhood, and that attacks of the disease are associated with a high degree of skin sensitivity to tuberculin.

4. In rare instances phlyctenulosis may occur in the absence of tuberculous infection, probably as a bacterial allergy to the agents of other diseases, particularly the granulomatous diseases, such as coccidioidomycosis. Very rarely it may be an allergic manifestation of exogenous infection of the conjunctiva and lid margins, particularly with Staphylococcus aureus.

5. The occurrence of phlyctenulosis in a child should be considered a warning of impending clinical tuberculosis and treatment should never be limited to local eye measures alone or to treatment during a single attack. A search should be made for active tuberculosis in the child's environment.

6. Local bacterial infection appears to be a factor in precipitating attacks of the disease in predisposed individuals, but there is no valid evidence to indicate that the bacterial infection is ordinarily causal in itself.

7. Efficacious therapeutic measures in the disease appear to fall into four categories: (a) Treatment directed against the tuberculous infection itself, as by desensitization with tuberculin; (b) dietary treatment, which probably reduces the activity of the tuberculous focus; (c) treatment designed to eliminate secondary bacterial infection of the conjunctiva and lid margins; and (d) treatment with cortisone, either topically or by subconjunctival injection, as a nonspecific method of aborting acute attacks. The effect of streptomycin and other antituberculous agents, such as promizole and para-aminosalicylic acid, should be explored in severe cases in which the cornea is affected.

8. Future research should be directed toward (1) uncovering the nature of tuberculosis-free phlyctenulosis, (2) discovering factors which serve to precipitate acute recurrences in phlyctenulosis patients, and (3) studying further those etiologic and predisposing factors already recognized.

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AN ANATOMIC STUDY OF THE PERIPHERY OF THE RETINA*

PART I. NONPIGMENTED EPITHELIAL CELL PROLIFERATION AND HOLE FORMATION

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We have become increasingly interested in the study of the periphery of the retina especially in correlation with detachment of the retina. In recent years considerable work has been done, particularly by Schepens and Bahn,[1] on clinical methods of examination of the periphery of the retina.

We have been fortunate in having a large supply of human eyes in The Eye Bank, and undertook our study with this material.

In the past, anatomic study has been based mostly on observation of microscopic slides and attempts at reconstruction by serial sections.

Our method was adapted from Troncoso's[2] micro-anatomic method of slitlamp study. With the low power of the binocular microscope, a detailed survey can be made of the periphery of the retina. With the higher power, quite fine details can be observed. The narrow beam of light is useful in differentiating retinal hole formation from thin-walled cysts.

After a lesion is located by this method, paraffin serial sections can be made for microscopic study. In this way, minute lesions are easily picked up and can be correlated with the general picture of the anatomy.

The material, normal human eyes, was obtained from The Eye Bank for Sight Restoration, Inc. These had been used for the most part as donor eyes for corneal grafts and then were fixed in Bouin's solution and preserved in 80-percent alcohol. The eyes had been fixed from a few hours to 48 hours after enucleation in the majority of cases. The side windows were cut and saved for the micro-anatomic study, while the central calotte was sectioned for general routine histologic examination.

When the vitreous was clear, the periphery of the retina was easily visible. When the vitreous was cloudy, it had to be removed to observe the retina. If the vitreous did not come away in one piece, it was removed piecemeal. All specimens, in which manipulation caused any retinal damage, were discarded.

NONPIGMENTED EPITHELIAL-LIKE CELL PROLIFERATION

In this part of our report, our discussion is limited to one form of pathologic change, which is a kind of cellular proliferation to be found at the periphery of the retina, and which may have some bearing on the etiology of detachment of the retina.

This kind of pathologic process is presented in three forms: (1) Granular patches, (2) floaters, and (3) holes. The latter two develop from the first.

The granular patches and holes are usually found in the peripheral portion of the retina within three to five mm. of the ora. The floaters are mostly found in the vitreous close to the ora serrata, the pars plana, and the periphery of the retina.

Among 101 persons (167 eyes) who have been examined, we found 38 persons who had this kind of anatomic change; 11 had both eyes involved. Among them were three cases of operculated holes and one case with a hole that had become organized.

In fixed preparations of the retina, the granular patches appear dry, grayish, and opaque with a granular surface. They are oval or elongated in shape and irregular in outline. Their size varies from a few micra to 2.5 by 0.5 mm. The longer axis is arranged usually in the meridional direction

* Under the auspices of The Eye Bank for Sight Restoration, Inc. Aided by a grant from the Milbank Memorial Fund.

of the eyeball. Often there are quite a few at the margin of the ora.

The appearance of the floaters is very similar to that of the granular patches. They are definitely developed from the granular patches, and it can be demonstrated that the granular patch separates from the retina gradually and is set free into the vitreous as a floater.

Floaters are grayish, rounded, and bud-like. They may be composed of one, two, or more clusters. Often cystoid spaces are present in the center of the floater. Before floaters separate, they always become oriented toward the anterior aspect of the eye and follow the direction of the zonular fibers. They appear to be attached to fibers similar to zonular fibers or to the fibrillas of the vitreous.

In seven cases out of the 38, floaters of the same kind were found without granular patches. It is assumed that they arose from a part of the eye that was not examined, or the floater was so small that the retina healed without a trace.

The third type of change noted consisted of holes of different forms. Hole formation resulted from the separation from the retina of the proliferated cellular masses. They usually separate en masse; perhaps this is the reason why they are not easily found in specimens of early detachment of the retina.

When the cellular proliferation involves the whole thickness of the retina, the result is a perforated hole. When only the inner layers of the retina are involved, the degenerated area of the retina remains without complete perforation.

In the process of separation, the edge may look like a hole partially covered up with an operculum or it may look like a hole with a granular border. At times it is impossible to determine whether perforation is complete, even with the help of the slitlamp. Only by microscopic study can one be sure.

Histologic study of the retinal lesion discloses small masses of proliferated cells which appear mostly in the inner layers of the retina and sometimes extend into the outer layers. Their nuclei are not like glial cells; they are larger, granular, less stained, and oval in shape. Sometimes clear nucleoli can be seen. The cytoplasm is larger in size and oval in shape.

The appearance of these cells is similar to the nonpigmented epithelial cells of the ciliary body. In one case these cells were seen as the continuation from the nonpigmented epithelium of the pars plana.

There is no ganglion-cell layer or inner plexiform layer overlying it. There may be a thin lining membrane which is either the interlimiting membrane or the nerve-fiber layer.

The granular patches have a tendency to form local adhesions with the adjoining vitreous. This is found in some of the gross specimens and also in most histologic preparations.

The adhesions consist of fibrils or zonular fiberlike structures extending from the proliferated cells into the vitreous. The association of fibrils with some superficial cells in the granular patches resembles the zonular fibers of the nonpigmented epithelium of the pars plana.

The retinal tissue underlying and surrounding these cellular masses is often degenerated. The area of degeneration in the retina may be limited to very superficial layers of the retina or may involve the whole thickness. When this occurs, a perforated hole results. The edge of the hole is round or oval in shape due to gliosis.

Histologic study of selected cases

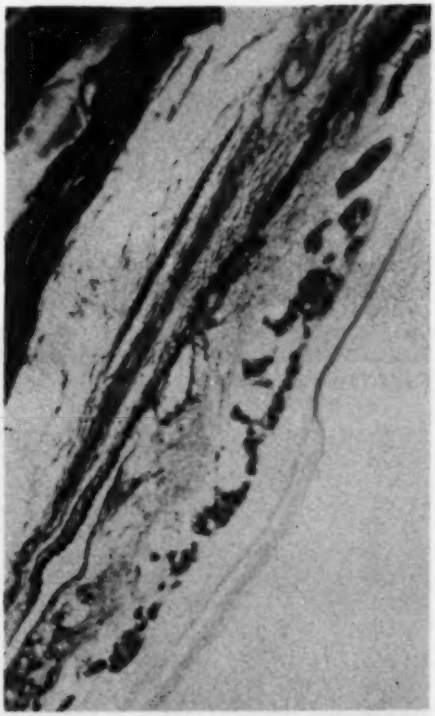
Case 1

(EB1553-O.D.). A man, aged 92 years, died of generalized arteriosclerosis.

A. *Gross.* There is an elongated, narrow, band-shaped patch, with a granular surface 2.5 by 0.5 mm. in size which begins at the very margin of the ora (fig. 1).

B. *Microscopic.* The surface is covered by an irregular layer of epithelial cells, one to five cells thick. The tissue below this layer is disorganized, with only a few nuclei

Fig. 2 (Teng and Katzin). Section of the granular patch seen in Figure 1, showing irregular proliferations of nonpigmented epithelium with cystoid degeneration underneath.



of Müller cells remaining. There are edematous and cystoid spaces. At the anterior end, there are small, irregular proliferations of the pigmented epithelium which are often noticed in the normal retina at the ora.

Fig. 1 (Teng and Katzin). Elongated granular patch beginning at the margin of the ora serrata and extending backward 0.5 by 2.5 mm.

The epithelial-like cells appear to be a continuation of the nonpigmented epithelium of the pars plana. Furthermore, the margin between the ora and the pars plana is not very sharp.

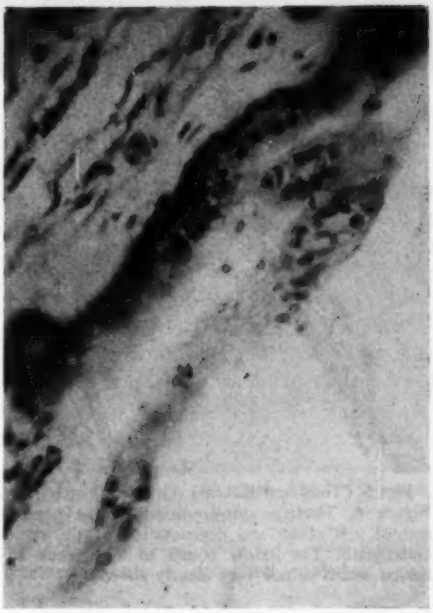


Fig. 3 (Teng and Katzin). High-power view, showing similarity between the nonpigmented epithelial cells of the pars plana and the granular patch.

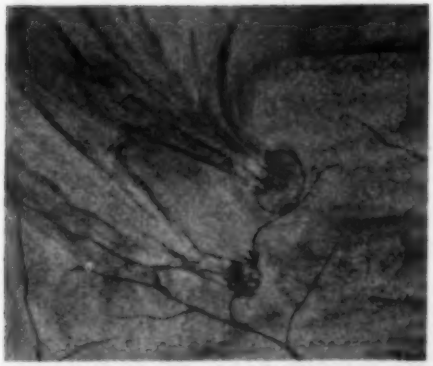


Fig. 4 (Teng and Katzin). Two granular patches with local vitreous adhesion.

Fig. 5 (Teng and Katzin). Granular patch from Figure 4. There is proliferation of the nonpigmented epithelium and degeneration of the retina underneath. The arrow points to a vitreous adhesion which is not very clearly shown.

There are fibrillas arising from the papillary parts of the granular patch. The fibrils all run in the direction of the zonule and form a local adhesion between the patch and the vitreous (figs. 2 and 3).

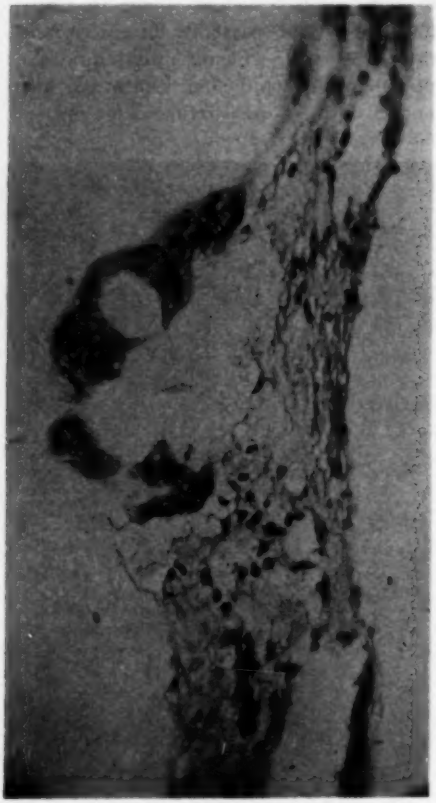


Fig. 6 (Teng and Katzin). High-power view, showing appearance of the nonpigmented epithelial proliferation.

CASE 2

(EB1709-O.D.). A man, aged 56 years, died of coronary occlusion.

A. *Gross.* There are two small granular patches at the periphery of the retina on the nasal side. Each measures about 0.5 mm. in diameter. One is 2.5 mm. from the ora. The second is 4.0 mm. from the ora. Each has a band of adherent vitreous originating from its surface. The surrounding retina is dis-

colored and degenerated; the areas of degeneration are 1.0 mm. in diameter in the first area and 0.7 mm. in the second. The surfaces are slightly elevated and granular or papillary in appearance. There is a small, linear area of pigmentation at the periphery of the second patch along a blood vessel (fig. 4).

B. *Microscopic.* There is moderately severe peripheral cystoid degeneration of the retina extending from the margin of the ora to one mm. distance from the first granular patch. There is proliferation of epithelial-like cells in the superficial layers and cystoid degeneration underlying and surrounding these patches. The tissue is replaced by glial cells. Although vitreous is not well stained, the local adhesions are easily made out (figs. 5 and 6).

FIG. 7 (Teng and Katzin). (Upper left) Two undetached floaters. (Lower right) One hole with a granular edge and an undetached floater on a degenerated patch of retina.

CASE 3

(EB1686-O.S.). A woman, aged 70 years died of congestive heart failure.

A. *Gross.* On the nasal side of the periphery of the retina there are two dumbbell-shaped granular masses attached to the retina about one mm. posterior to the ora. There is cystoid degeneration of the retina underlying and surrounding them.

In addition, about five mm. away and four mm. posterior to the ora serrata, there is another larger degenerated patch of the retina. In the center of this patch there is a protruding granular area about one mm. in diameter with a hole on one side. This is partly due to degeneration and partly due to separation of the mass from its origin in degenerated retina. In the same patch, posterior to the hole, there is another undetached floater. We regard this as clear evidence that the hole and floater develop from the same pathologic change in the retina (fig. 7).

B. *Microscopic.* Two floaters at an early stage are attached to the retina and there is local adhesion between the floaters and the vitreous. The epithelial-like cells are, for the most part, stuck together and form irregular masses. There are fairly large cystoid spaces underlying them. The underlying and surrounding retina is moderately disorganized and degenerated (figs. 8 and 9).

CASE 4

(EB1585-O.S.). A man, aged 41 years, died of coronary thrombosis.

A. *Microscopic.* Section of free vitreous floater reveals a detached mass of pro-

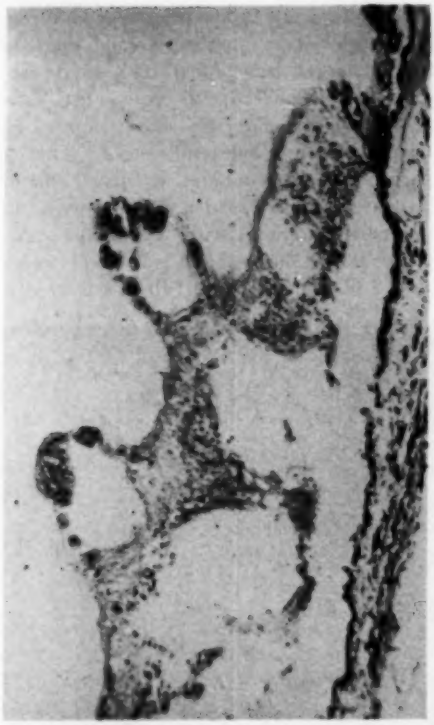


Fig. 8 (Teng and Katzin). Section of the two undetached floaters seen in Figure 7, showing the development of floaters.

liferated epithelial-like cells in the vitreous. Large cystoid spaces are present at the center of the mass, and the cells have nuclei which are less distinct and pale staining (figs. 10 and 11).

CASE 5

(EB1558-O.D.). A man, aged 45 years, died of bronchopneumonia.

A. *Gross.* The eye is normal except for one hole with a complete operculum and one with a partial operculum.

They are found about two mm. from the ora, in the peripheral part of the retina. In the first one the operculum is attached very tenuously at the peripheral anterior margin.

The second hole has an incomplete operculum which is more securely attached to the posterior edge (fig. 12).

B. *Microscopic.* The first hole was not sectioned. In the second one, the cellular appearance and the picture of degeneration of the retina are the same as the other sections. This specimen shows more tendency to coherence of the proliferated cells. Degeneration of the retina is quite marked but the lesion did not perforate.

There is no local adhesion to the vitreous at the anterior portion but it is visible at the posterior part of the mass (figs. 13 and 14).

CASE 6

(EB1749-O.D.). A man, aged 68 years, died of acute leukemia.

A. *Gross.* In a small patch of degenerated retina on the nasal side, there are two small,

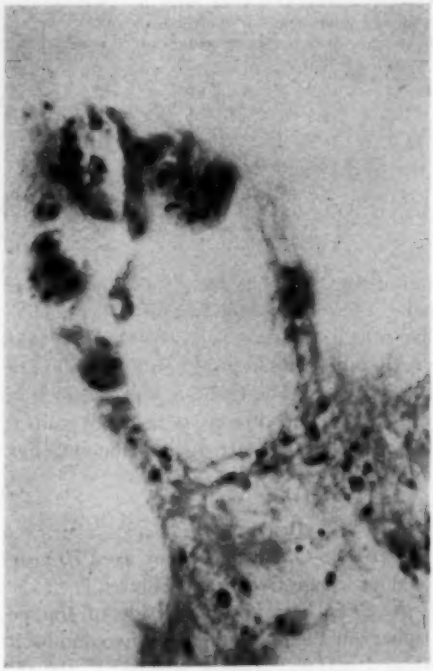


Fig. 9 (Teng and Katzin). High-power view, showing cellular characteristics of the undetached floater.

perforated holes, one of which is 0.3 mm. and the other 0.7 mm. in diameter (fig. 15).

B. *Microscopic.* Over the degenerated area of the retina, the structures are completely disorganized and cannot be distinguished in layers, having been much thinned out and replaced by glial tissue. There are a few cystoid spaces. The holes are perforations in the degenerated retina with well-defined fibrous margins and rounded edges.

Over the region of the hole there is a small area where vitreous is absent suggesting that the hole resulted from a vitreous adhesion (fig. 16).

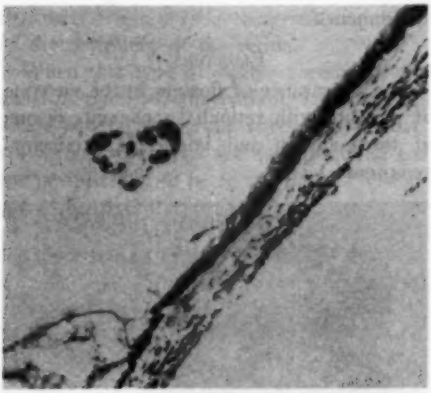


Fig. 10 (Teng and Katzin). Free floater in the vitreous.

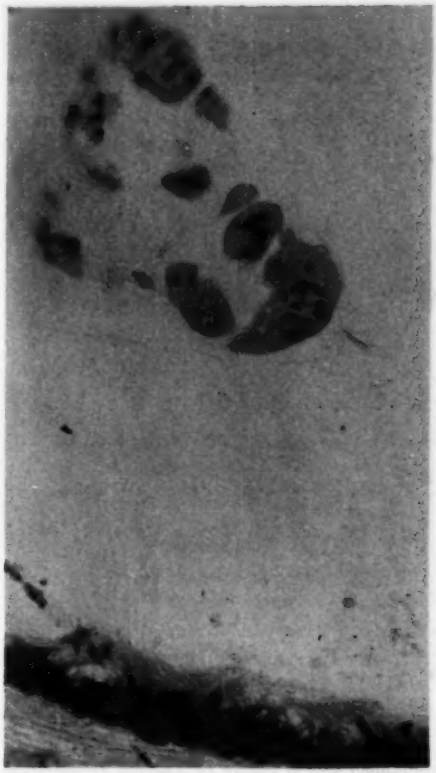


Fig. 11 (Teng and Katzin). Cellular appearance of the floater seen in Figure 10, with nonpigmented, epithelial-like cells.

Fig. 12 (Teng and Katzin). Holes with operculum.

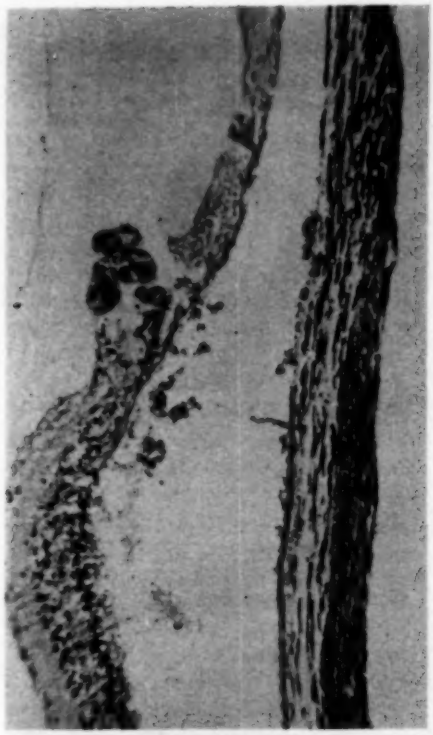


Fig. 13 (Teng and Katzin). Appearance of the operculum seen in Figure 12. There is degeneration of the retina and a hole without complete perforation.

Discussion

We believe that the granular patches observed in the peripheral retina during the course of this study developed from the presence of nonpigmented epithelial cells of the type normally present in the pars plana of the ciliary body. From our sections, there appears to be adequate proof of the nature of these cells. Their morphology is the same and they are intimately associated with zonular fibers.

The reason for the presence of these cells in the retina is not clear. We find that granular patches are much more commonly found on the nasal side of the retina where there are many more irregular folds during embryologic development.

The possibility suggests itself that they might be cell rests. (We have one eye from a child, aged seven years, with a cellular floater and a vitreous fiber attachment to the original site.)

Another possibility is that of a redundant fold of ciliary epithelium overlying retina where the teeth of the ora serrata are most highly developed. Occasionally pigmented cells are observed in the lesions. These are definitely not of inflammatory origin.

The type of floater described in this paper is certainly not the only one that exists, but the differentiation of floaters may be very valuable as an aid in the handling of retinal detachments.

Floaters

The appearance of floaters in the vitreous of patients with retinal detachments is one of the common and important prodromal symptoms.

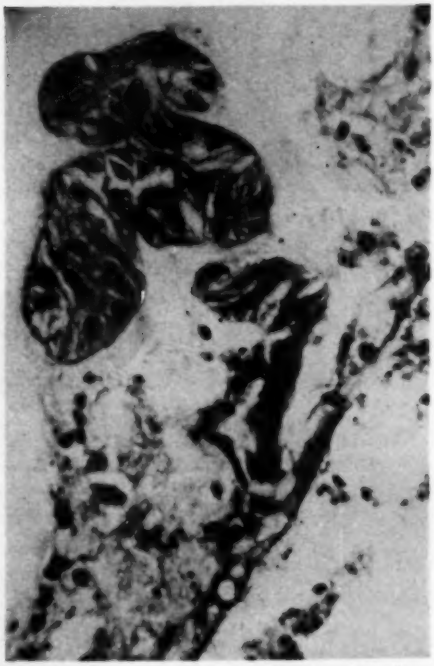


Fig. 14 (Teng and Katzin). High-power view, showing appearance of the cellular structure.

Samuels[3] was the first to notice spherical vitreous opacities composed of cellular elements, occasionally found in the vitreous, sometimes floating freely and sometimes attached to the retina or nervehead by a pedicle. He thought some of these opacities were proliferations of the glial cells while others containing pigment granules were derived from the pigmented epithelium.

These spherical floaters may be the same as the ones we noted. They are fairly common and are found overlying the anterior periphery of the retina and pars plana.

From the appearance of the undetached floaters and their histologic picture, it seems that their origin is from the granular patches of the periphery of the retina.

When this type of floater appears in the field of vision of the patient, it should indicate liquefaction of the vitreous. The floaters in our specimens are usually found too far peripherally to be in the field of vision.

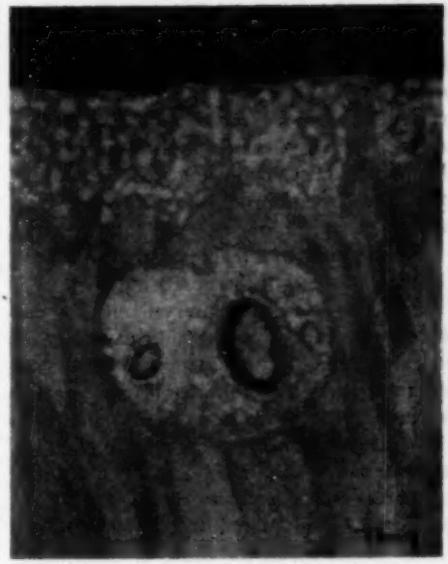


Fig. 15 (Teng and Katzin). Two holes on a patch of degenerated retina.

Holes without detachment

This last part of study refers to the anatomy and development of peripheral retinal holes without detachment of the retina.

Clinical observation of retinal holes without detachments has been reported by Knapp,[4] Arruga,[5] Vogt,[6] Sabbatini,[7] Jeandelize and Baudot,[8] Burch,[9] Genet,[10] Guillet,[11] Nico Trantus,[12] Hanssen,[13] and Graupner.[14]

The cases of Arruga, Sabbatini, and Genet show many pigment changes and they thought the lack of detachment of the retina in their cases was due to the presence of chorioretinal adhesions resulting from inflammatory change.

The rest of the cases, including all of ours, cannot be explained by this theory because there are no pigmented changes and no chorioretinal adhesions from inflammation.

From our experiences in this anatomic

Fig. 16 (Teng and Katzin). Section of a hole from Figure 15, showing degeneration of the retina and replacement with glial cells.

study, we have learned that sometimes it is very difficult to differentiate small cysts of the pars plana, dilated cysts due to peripheral cystoid degeneration, and small degenerated areas of the retina, from real holes in the retina, even with the help of the slit-lamp. In clinical ophthalmoscopic examination, therefore, it would be even more difficult.

Small granular patches are usually located in the periphery of the nasal side of the retina and they can be observed only by indirect ophthalmoscopy if the magnification is great enough. There are some cases in the literature which are similar to ours, as for example, the fifth case of Knapp in which he described a hole with a granular edge; his case actually developed detachment of the retina later on.

For correlation of other factors besides hole formation, in the cause of detachment of the retina, we have reviewed the literature on the pathology of fresh detachments of the retina. This has been reported by Kronfeld,[15] Kümmell[16] Veil, Dollfus and Designes,[17] Vogt,[18] and Sourdille.[19] The retinal holes reported by several of these authors are very similar to those in some of our cases.

The holes were rounded at the edges and were found in an area of atrophied retina with some irregular cystoid spaces. Many of them had adhesions between the vitreous and the degenerated retina or the operculum of the hole. The detached operculum of Vogt's case is very similar to our case with a floater in the vitreous. There were no inflammatory signs or chorioretinal adhesions reported in these lesions.

Kümmel had mentioned that, in his case, there was some epithelial proliferation on a small scar, but he did not make any correlation between epithelial proliferation and hole formation.

Naturally, all of the specimens collected by these authors were in a more advanced condition, due to detachment of the retina and surgical treatment, and were, therefore, not so easily examined as ours. It is pertinent too, we think, that the same method of study was not used for establishing the mechanism.

An analysis of the literature on retinal detachment calls to mind the words of Gradle,[20] who said: "The challenge of retinal detachment is the enormous complexity of the entire problem. The present-day knowledge of this pathologic entity, incomplete as it is, more than suffices to fill a large volume, but still contains large gaps."

It is also obvious to everyone who reviews the literature, as pointed out by Duke-Elder, that it is enormous in quantity but confusing.

We can only assemble the points of agreement of all the authors on this subject to formulate a theory on the mechanism of detachment. This may be useful in guiding us to further investigation especially in regard to holes without detachment.

Mechanism of detachment of retina

The mechanism of detachment of the retina (idiopathic type) is well summarized by Knapp,[4,21] Arruga,[5] Elwyn,[22] and Duke-Elder.[23] These authors agree on certain essentials. The factors which lead to detachment may be summed up in these categories: (1) Changes in the retina, (2) adhesions of the retina, (3) adhesions of the vitreous to the retina, (4) changes in the vitreous, (5) trauma, and (6) movement involving traction on the retina.

"The retina stays in position partly because of capillary attraction between the two layers and largely because of the influence of the intraocular pressure distributed uniformly through the vitreous body pressing it from within on the retinal pigment epithelium" (Duke-Elder).

Duke-Elder states that the choroid is more easily ruptured than the healthy retina, and Croll,[24] saw more tears of the choroid in war injuries than tears of the retina.

Vogt[6] further insisted that degenerative changes must be present in the retina before a rupture can take place. Most authors regard cystoid degeneration and nutritional

disturbance of the retina as the causes of degenerative changes.

Leber,[25] observed that rupture of the retina usually occurs at the place where adhesions between the vitreous and retina have taken place. This theory was accepted by Gonin,[26] Lindner,[27] and Boeck.[28]

Boeck described adhesions between the margin of the hole and vitreous in two cases. We noticed that this local adhesion plus the motility of the vitreous may cause degeneration of the retina and separation of the proliferated mass of nonpigmented epithelial cells.

The vitreous changes that have been noted in separation of the retina are: (1) Liquefaction, (2) shrinkage, and (3) detachment.

It is generally accepted that liquefaction of the vitreous is an important factor in retinal detachment. von Sallmann confirmed the fact in every one of his cases. Shrinkage of the vitreous was described by Gonin and confirmed by Lister,[29] Lindner, and von Sallmann.[30] Detachment of the vitreous was observed by Benziger, Pillot, Lindner, von Sallmann, and Vogt.

Compos and Raffael[31] brought out that detachment of the vitreous is commonly seen in myopic and senile eyes and has little to do with detachment of the retina.

Best[32] pointed out that, with every movement of the eyeball, the vitreous undergoes movement and exerts a force of traction at the adherent parts of the retina and vitreous.

Liquefaction of the vitreous will naturally increase its mobility. Posterior detachment and shrinkage of the vitreous will create a greater opportunity for agitation during the movements of the eyeball. Lindner stressed that rotating and whirling movements of the eyeball are the worst kind.

If the retina is already weakened, due to degeneration or other causes, and local adhesions exist, particularly in the presence of liquefaction of the vitreous, the slight force of movement may precipitate hole formation. Liquefaction of the vitreous, according to Arruga, associated with ocular movements, compels the vitreous to strike the edge of the hole, thus forcing the vitreous behind the retina.

In a similar hypothesis, Pischel[33] regards the hole as a new route for the flow of intraocular fluid. This flow is facilitated by frequent elevation of one retinal lip by the pull of a vitreous adhesion. Rotation of the eyeball forces this fluid further under the lips of the tear, steadily increasing the spread of the detachment.

Summary

1. A kind of cellular proliferation of cells that resemble nonpigmented epithelium in the periphery of the retina has been observed in 49 out of 167 supposedly normal eyes of 38 persons out of 101.

2. At the peripheral areas of the retina, there are usually formations of local adhesions between the retina and vitreous by fibrils adherent to the epithelial cells.

3. There is usually cystoid degeneration and atrophy of the retina below and around the mass of epithelial proliferation. This varies in degree.

4. A tendency to separation of the proliferated cells en masse has been observed. The result is the formation of a floater into the vitreous.

5. As to hole formation—when the granular patch is partially separated from the retina it may give the appearance of a hole with an operculum.

If it is a complete separation and involves the whole retinal thickness and is well fibrosed, it will look like an oval hole with a round edge on a thin or degenerated area of the retina.

If the mass involves only the inner layers of the retina, the separation will result in a small, degenerated patch.

6. As to the total number of holes seen—in our collection, three cases show holes with opercula and one case has two well-organized holes.

210 East 64th Street (21).

We are indebted to Dr. Algernon B. Reese for his kind interest in this study and his evaluation of the pathologic material.

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PATHOLOGY OF THE RETINOPATHY OF PREMATURITY: RETROLENTAL FIBROPLASIA*

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The retinopathy of prematurity is a common cause of blindness in the preschool age. Clinical and statistical reports of this disease, so intensively studied by Terry, have been numerous the past decade. (Our oldest specimens date back 37 years.) Few microscopic studies of the early and definitive stages have been made.

This report is based on a study of the early definitive and successive stages of ocular and general histopathology, both before and after clinical recognition. The material which depicts early states of the disease was obtained at autopsy; that illustrative of later stages was derived by enucleation from patients suspected of harboring neoplastic growth. Two previous studies have shown the relationship of this entity to a number of confusing, imitative ocular diseases which occur in both premature and mature infants as well as in juveniles and adults.[1, 2]

My studies of this retinopathy indicate that it appears in three characteristic histopathologic phases. These may be related to similar clinical classifications. The three states of the disease are: (1) The primary retinal disease; (2) the secondary retinal disease—from vitreous organization; (3) ocular atrophy—from late repair.

These three states of the retinopathy will be described and illustrated from histopathologic material. Each has been observed clinically, and postmortem correlations have been made.

THE PRIMARY RETINAL DISEASE

The earliest ocular signs of the disease were recognizable only microscopically and were specific. They occurred bilaterally in the anterior incompletely differentiated retina at its oral insertion. The histopathologic signs were edema and dilated capillary channels and, commonly, endothelial proliferation and hemorrhage.

These disassociating elements could be found within a day of birth though they might not develop until weeks later. Signs of cellular inflammation were absent. Involvement of the oral retinal ring was not uniform, some meridians escaped, while the temporal regions generally showed more edema and erupting vascular tissue.

An outstanding finding of the early primary retinal stage was incompleteness of differentiation of the oral retina. The inner limiting membrane was characteristically absent or markedly underdeveloped at the anterior attachment of the retina, and a few other areas, somewhat posteriorward, showed thinness and incompleteness. This was seen clearly in stained sections, also in unstained sections examined by phase microscopy.

Mueller's supportive tissue was relatively absent in the zone of rapid growth at the oral insertion. The insertions of the retinas in premature infants generally are redundant and well anterior, often as far as the ciliary body or its processes. This vulnerable, incompletely differentiated tissue lies in a zone of rapid and unequal growth.

The oral fold (Lang's) may contain some hemorrhage. Only most rarely was random hemorrhage found other than in the oral region and then not associated with hamartomatous vasoformative tissue (figs. 1, 2, and 3).

In general, the retinas away from the ora were differentiated according to fetal age. Ganglion cells were present, as well as outer and inner nuclear layers. The rods were well represented.

* From Massachusetts Eye and Ear Infirmary, Pathology Laboratory. This study was made possible by a grant from the Kresge Fund for Eye Pathology.

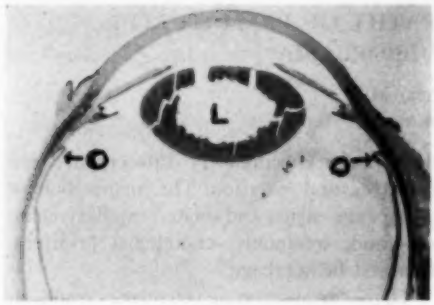

Fig. 1 (Heath). Male infant born two months premature (birth weight two lbs., two oz.). The mother had bleeding beginning the third month, twice severe enough to require hospitalization. During the second hospitalization the membrane ruptured spontaneously and amniotic fluid leakage continued for over two months until time of birth. After birth, the infant's weight dropped to one lb., 13 oz., and then gradually rose to five lbs. nine weeks later. During this period, the child was anemic, with low hemoglobin but had a satisfactory reticulocyte count. On the day before death his weight was six lbs. and three oz. Six hours after a satisfactory feeding, when he appeared in good condition, the child was found dead.

The gross general and microscopic postmortem diagnoses were: acute early pneumonitis; septicemia (streptococcus viridans and streptococcus alpha-hemolyticus); cerebral edema. Sepsis was the immediate cause of death. There was no evidence of vascular malformation in the brain, meninges, or viscera.

Horizontal section, anterior segment, right eye. (O) Oral loop of retina. (L) Infant lens. Grossly and clinically the eye was relatively normal.

In the posterior retina an occasional capillary was found ruptured through an incomplete internal limiting membrane, thus exposing the vitreous to hemorrhage. Such a small amount of blood in the vitreous, isolated and without recurrence, apparently was a local phenomenon. Small local hemorrhages within the retinal substance at this age would be no more significant than in older patients, and absorption would be rapid.

During the primary stage, reversibility and resolution of the whole process probably are the rule. The premature infant, however, is afflicted with a susceptibility

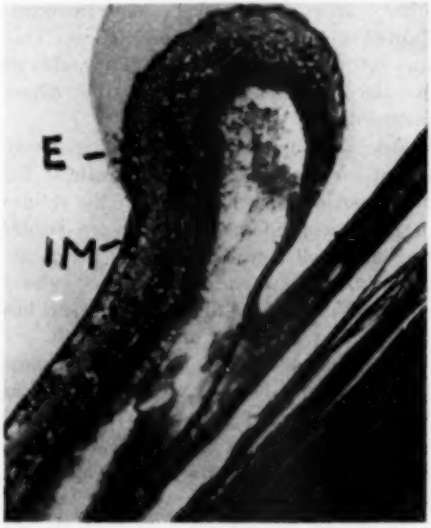

Fig. 2 (Heath). Magnified loosely coapted loop of retina of Figure 1 attached to pars plana of ciliary body. (E) Note early edema of inner layers. Slight hemorrhage in and under loop. (IM) Incomplete inner limiting membrane.

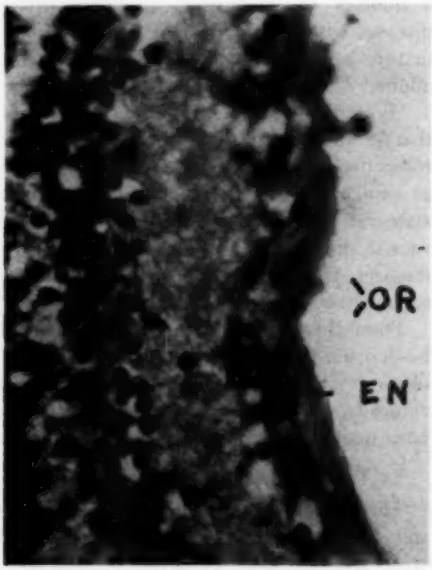

Fig. 3 (Heath). The typical undifferentiated edematous oral loop of retina. (OR) Absent internal limiting membrane or Müller's fibers. (EN) Early endothelial proliferation.

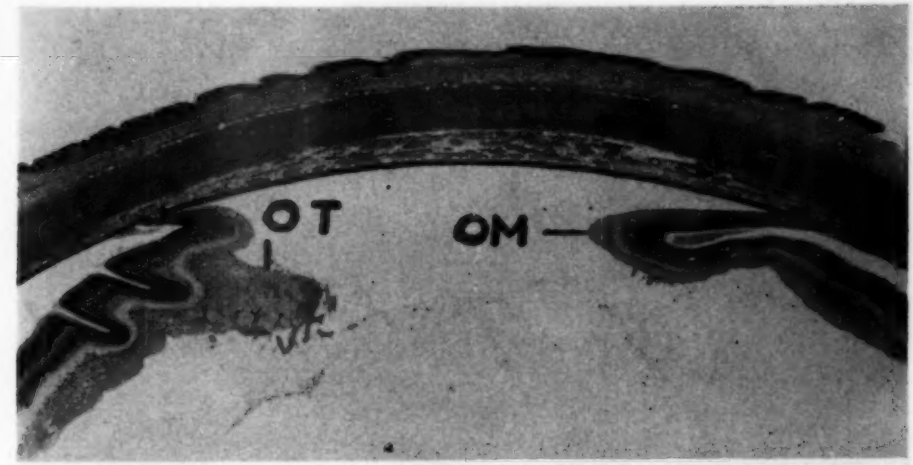

Fig. 4 (Heath). Another meridian of the same eye as in Figure 1. (OT) Oblique section of temporal ora shows extensive edema and early neovascular tissue. (OM) Mesial ora, showing earlier edema and slight hemorrhage.

toward continued leakage of protein-rich serum and blood from the anterior retina because of weakly supported proliferating neovascular tissue and relatively high blood and capillary pressures (fig. 4).

Endothelial cells in knots and buds in active proliferation were remarkably constant, and resembled a hamartomatous growth within the inner layers of the retina (figs. 5, 6, and 7); gliosis was secondary. In many sections protein-rich edema was extensively present on the anterior face of the hyaloid.

Early organization of the vitreous clearly emanated from the ora. It was brought about by successive seedings posteriorward by edema, blood elements, and fibrocytes (figs. 8 and 9).

A correlation of microscopic findings with those seen clinically with the ophthalmoscope was possible only after posterior extension of the disease. The lines of fine dots seen in the vitreous with the ophthalmoscope proved in sections to be hemorrhage. The delicate trabeculas and fuzz-outlined strands which developed later proved to be further advances in the organization of the vitreous. Coarser strands and bands

Fig. 5 (Heath). Higher magnification of partially differentiated ora on temporal side. (ED) Marked edema of inner layers. (EN) Endothelial proliferation in knots. (EB) Erupting neovascular tissue derived from endothelium. (IM) Incomplete internal membrane.

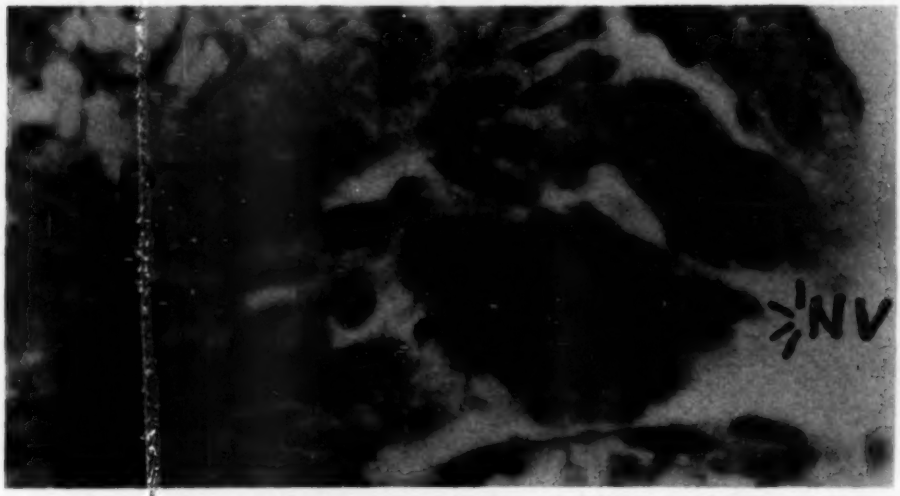

Fig. 5 (Heath). High-power detail of the proliferating endothelial cells (EP). Newly forming capillaries (NV).

Fig. 7 (Heath). Oral loop in the retinopathy of prematurity with marked proliferative activity of neovascular tissue (NV_1) due to endothelial budding where the retina is more edematous, loose and undifferentiated, and consequently less restrictive. (NV_2) A less explosive neovascular proliferation where the oral retina is more compact and possesses a firmer structure partly held by an internal limiting membrane. Gliosis is not characteristic of the earliest states.

caused traction associated with opaque areas. Extension of the organization was indicated by folds of the retina. These changes found microscopically and clinically need not be elaborated since they are a natural sequence of events representing vitreous organization.

Reversal rarely occurred clinically once the vitreous was moderately organized. The retina rarely showed a fixed partial displacement in one meridian. In this case, the retinal leak was stopped. The late and final result of such reversal would depend upon the degree of organization. A limited retinal separation was indicated by falciform folds, just as in other retinal diseases.

The choroid and ciliary body in sections showed marked congestion but possessed compact structure and avoided disrupting edema and hemorrhage. The iris vessels were relatively thick-walled and impermeable.

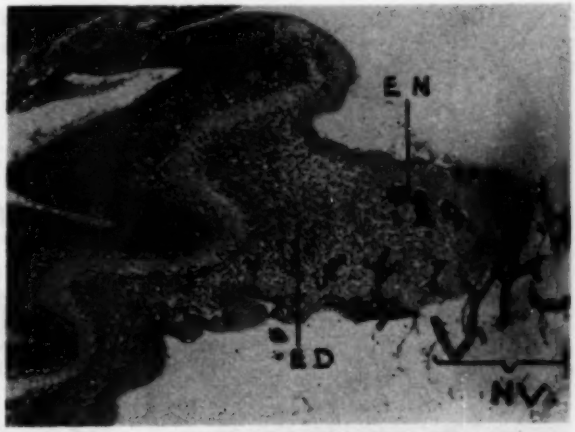

Fig. 8 (Heath). Temporal ora of three-month premature infant showing marked edema (ED), proliferating endothelium (EN), and a tangle of new capillaries (NV), derived from the focal endothelial proliferation, entering the vitreous. Repeated ophthalmoscopic observations since birth only showed dilatations of the retinal vessels.

Secondary retinal disease from vitreous organization

Both clinical and miscroscopic studies showed that, after there were secondary retinal complications from the rapidly evolving vitreous organization, the whole process did not reverse short of retinal separation. The fibrillary fetal type of vitreous is a natural vehicle for organizing the leakage from the oral tangle of dilated capillaries and neovascular tissue (fig. 10).

Microscopically, vascular tufts appeared in the retina posteriorward (fig. 11). These entered the retina from its inner surface but their origin usually was anterior. Separation of the retina became inevitable as these contractile organizing fibrillas and bands pulled on this structure (fig. 12).

The postlental fibrosis and glial proliferations incorporated and dragged axially and elongated the ciliary processes within a dentate membrane. This is the retrolental membrane seen clinically. With organization of the vitreous, the retina itself inevitably was drawn inward and somewhat folded. Hemorrhages and some necrosis were seen in sections.

Newly budded capillaries and well-established small vessels were formed in the inner layers of the retina. From elaboration of this exaggerated repair and fibrosis the retina soon became bunched or balled behind the lens (fig. 13). The excessive vascular congestion in the uvea disappeared as the retina became separated.

Some nonspecific cellular inflammatory infiltrations were found to occur with retinal separation. Though involvement was bilateral, there were unilateral differences in the degree of the pathologic process.

Only the early histopathology of the secondary vitreous stage of the retinopathy of prematurity is characteristic and specific. The late phases of the histopathology after retinal separation resemble that found in both juvenile and adult eyes which have been subjected to repeated extensive vitreous hemorrhage. In other words, late phases of

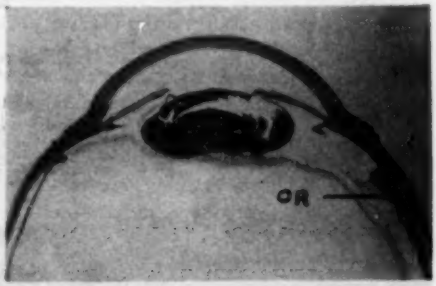

Fig. 9 (Heath). Anterior segment cut horizontally. The oral retina on one side (OR) presents extensive edema within the loop and escaping into the vitreous in company with neovascular tissue.

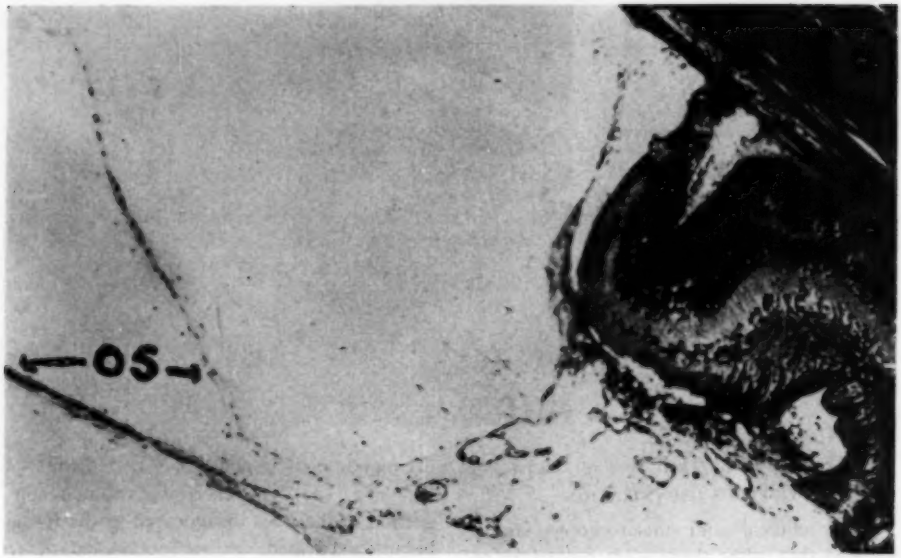

Fig. 10 (Heath). Higher power view of Figure 9. Note early fibrovascular vitreous organization, with strands (OS) extending inward and posteriorward. Not recognized clinically although looked for repeatedly.

retinal separation, due to one of many causes, tend to resemble each other.

Clinical Notes of Primary and Secondary Retinal Stages

Clinical observations with the ophthalmoscope in the early stages show dilated retinal vessels. After indentation of the sclera by a muscle hook near the ora, one can see in some cases with difficulty gray zones of lost retinal transparency, some hemorrhage, and evidence of neovascular growth.

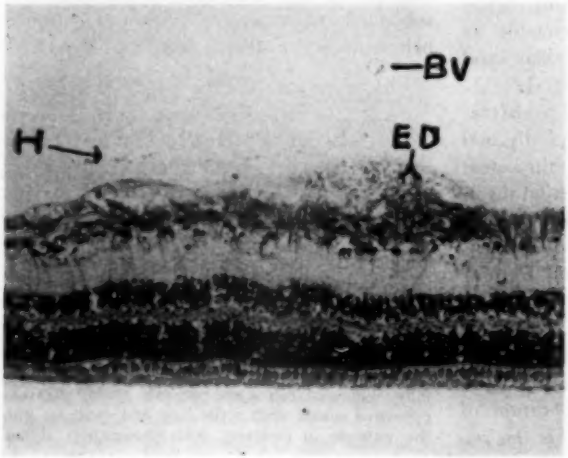

Fig. 11 (Heath). More posterior zone of the retina at an early stage of vitreous organization. Edema of superficial inner layer and interrupted inner membrane (ED). Thin, dotlike line of erythrocytes in the vitreous (H). Newly formed capillary tube (BV).

In the second stage, that of vitreous organization, one sees develop over a period of days or weeks, from collateral dustlike opacities which coalesce in fine fibrillas, strands of fibrous material extending posteriorward. In very rare instances a retinal fold or stalk is formed and the process spontaneously becomes arrested. Occasionally retinal contractures and striae can be seen at the nervehead.

Late repair and atrophy

The late stages of this disease were microscopically characterized by massively separated retinas exhibiting contracted blood vessels, marked atrophic and degenerative changes. Necrosis and reparative fibrosis, pigment proliferations, and mineral deposits were common.

Fig. 12 (Heath). A still later stage than Figure 11 of a posterior organized vitreous. A firm contracted strand (VT), visible with careful ophthalmoscopy, inner limiting membrane (IM).

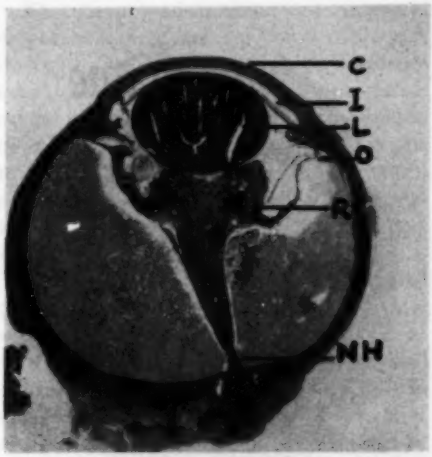

Fig. 13 (Heath). Enucleation at age nine months. Advanced stage of vitreous organization and secondary separation of the retina. (C) Cornea. (I) Iris pushed forward over angle. (L) Lens well forward. (O) Oral attachment of retina. (R) Retina with early anterior membrane. (NH) Nervehead dragged inward.

The fibrosis was often exaggerated within the retina and behind the lens. The latter structure often was pushed forward by a posterior constricting and shrinking hammock across the ciliary ring. The ciliary processes which were seen behind the lens had been drawn in axially and combined with fibrous tissue to form a dentate fibrovascular structure. The ciliary body itself was sometimes drawn in.

The iris often presented anterior and posterior adhesions. The anterior chamber was rendered shallow, the lens at times had touched the cornea. Glaucoma was a frequent clinical complication from iris-block of the filtration angle; sometimes hypotony was present.

In sections the retinal blood vessels appeared narrow and many had hyalinized walls. Collections of macrophages, many of them carrying lipids, lay just outside the retina or between the separated retinal layers.

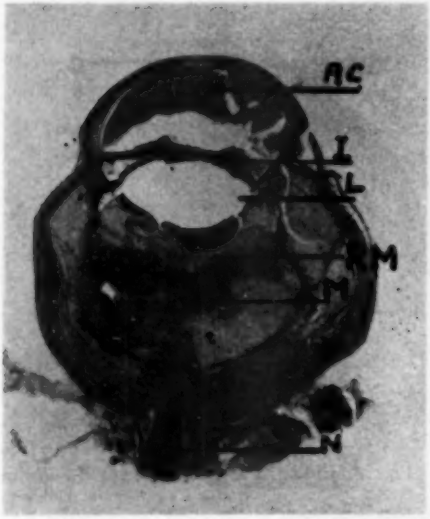

Fig. 14 (Heath). Enucleation at age four years. State of phthisical atrophy with advanced pathologic repair. (AC) Anterior chamber deepened. (I) Iris. (L) Lens drawn posterior. (RM) Fibrous retrolental membrane. (M) Extensive gliosis and cholesterin clefts. (S) Sclera. (N) Atrophic optic nerve.

Cholesterin was frequently part of the repair process, seen in this stage of the retinal pathology as clefts. Large and small cysts were common. Vessels with substantial walls lay in the organized fibrous sheath behind the lens.

With late shrinkage of the globe, also part of the repair process, the anterior chamber had deepened because the lens had been drawn posteriorward by cyclitic membrane. The lenses often showed cataractous changes. In a word, the late stage represented pathologic repair and atrophy, summarized by the term phthisis bulbi (fig. 14).

Study of Eyes from Infants of Premature Birth

For comparison, a study was made of eyes from stillborn prematures ranging from three months to full-term in age. The stillborn specimens showed some edema and occasional hemorrhages in the retina but no significant herniating neovascular tissues were found in the premature group.

In the oral zone capillary structure was relatively sparse. The endothelial cells were smaller and less deeply stained. The nuclei showed less chromatin structure. The inner limiting membrane stopped near the point at which the retinal loop began, and Müller's fibers were absent. The retinas of the premature infants in general were also inserted well anterior, sometimes on the pars plana and ciliary body. No doubt some stillborn prematures were candidates for retinopathy of prematurity. Retinopathy of prematurity not only is proportional to the degree of prematurity but obviously requires continuance of life to become fully manifest.

General Postmortem Studies in Retinopathy of Prematurity

The findings from a number of postmortem examinations varied greatly. In most instances little change other than the immediate cause of death and prematurity was found. In others, extensive hamartomatous vascular changes in the leptomeninges over the base of the brain and cervical cord involving some of the ventricles, the pons, with some obstruction and hydrocephalus, and a diffuse cerebral deficiency were found. Only a few manifestations of encephalo-ophthalmic dysplasia were observed.

Discussion

The early stages of this retinal disease are not satisfactorily seen with the ophthalmoscope. But by indenting the sclera near the oral retina, some changes in the anterior retina may be noted by direct, and better by indirect, ophthalmoscopy. These changes are congested vessels and gray patches of edema punctuated by hemorrhage; for complete details microscopic examination is necessary.

Normal infants sometimes show grayish areas at the oral loop and small random birth hemorrhages, but no retinal neovascular proliferations and no vitreous involvements were noted. It is conceivable that some of the retinal changes already described can origi-

nate apart from prematurity and be found in older children. The edema and hemorrhage are, however, limited in degree and extent and are nonprogressive, hence a destructive organization of the vitreous is avoided. Complete reversibility of such a minor process is the rule. In the premature, the retina is quickly pulled apart by the organizing fibrillary vitreous.

The question, "Is retinopathy of prematurity a new disease?" can be answered in the negative. We have specimens in the laboratory dating back over 30 years. In the past, specimens usually were described and catalogued from late stages, and numbers of mimicking diseases were included.

We know now from microscopic study that only the early states of the retinopathy of prematurity present a completely distinctive pathologic picture. We also know that certain nongenetic and acquired fetal ocular diseases in their late stages simulate true retinopathy of prematurity.

The higher survival rate of premature infants was obtained about 20 years ago, while only the past decade has shown an apparent increase in the retinopathy of prematurity. This lag between the achievement of higher survival rates of premature infants and the apparent increase of retinopathy of prematurity has not been explained by any statistical studies to date. Among the areas investigated statistically are those relating to the mother's health, the over-all management of the premature in different cities, and miscellaneous factors.

From clinical studies in various parts of the country, apparent wide local variability in incidence and apparent differences in collateral diseases accompanying retinopathy of prematurity have turned up. Since there is a direct linkage between the degree of prematurity and the incidence of retinopathy, it should follow that local manifestation would be relatively constant provided management was also relatively similar. I have only some suggestions relating to the apparent statistical discrepancies.

The sharp local increase one year and decrease the next are suggestive of an epidemic. Cases in areas of high incidence usually are accompanied by multiple extraocular pathologic conditions. This suggests, of course, that the apparent increase is due to another simulating disease—for example, a nongenetic congenital disease, usually maternal in origin, which in its late stages simulates the retinopathy of prematurity.

Fetal rubella cataract, which is an isolated or epidemic expression of ocular disease acquired during the organogenic period of fetal life and is coupled with heart and central nervous system involvement, falls in this category. Sporadic ocular diseases have many causes. In this connection it may be said that accurate early diagnosis is the key to accurate statistics.

The average over-all incidence of between 15 and 20 percent of retinopathy of prematurity is at least in part coupled with the proved survival rate by low-weight, early premature infants.

From our studies of ocular tissue and postmortem study, we have been able to establish that the primary location of retinopathy of prematurity is in the oral retina, a zone of rapid growth and of least differentiation; that the loose and weakly supported retina contains a newly forming vascular tissue; that this metabolic ensemble has the potential for proliferation of an erupting, leaking vascular structure; that this manifestation can appear at birth; that the disease is proportional to the degree of prematurity; and that within the eye there are predisposing factors of structure and altered physiology.

The precocious proliferation apparently has some relationship to a lack of inhibiting factors from endocrine sources. Some of these factors may be discoverable.

Obviously a delicate balance exists between enough structural completeness to contain embryonic budding vascular tissue and the adaptability requirements of growth. The sudden functional demands of

premature birth must at times prove excessive to this balanced ratio and inevitably cause some eruption. A relatively high intravascular pressure and absence of inhibiting factors tip the scale. It is likely that an incidence of 15 to 20 percent of retinopathy is an expression of failure to meet this balance.

A further hint as to the accuracy of these conclusions is derived from a study of stillborn infants of various ages, who show some hemorrhages in various parts of the retina. The differences between these random hemorrhages and those of the retinopathy of prematurity are, on the one hand, a contained limited hemorrhage, and, on the other, the continued leak into the vitreous from a growth zone incapable of containing it.

Microscopic examination by several methods confirms the incompleteness of the retinal structure and proves that denser tissues elsewhere in the eye escape the oral changes. Not only does the growing, congested neovascular retina favor pathologic permeability but the fibrillary fetal structure of the vitreous encourages organization. It is obvious that this fibrosis, retrolental or elsewhere, is a secondary manifestation responsible for the irreversible massive separation of the retina.

Conclusions

As a general rule, the retinopathy of premature birth occurs proportionally to the degree of prematurity. Microscopic characteristics of the disease can be found at birth or shortly thereafter. Clinical recognition may be delayed for months. The origin of the disease is retinal and bilateral, and the usual site is the oral zone.

The histopathology of the retinopathy of prematurity is found in three states which are illustrated herein.

1. *The primary retinal disease* is characterized by edema and some hemorrhage in an incompletely differentiated retina at its oral attachment. It is associated with marked congestion of the uvea. Endothelial proliferation and budding and the development of neovascular tissue superficially placed in the anterior oral loop of the retina are characteristic. Signs of cellular inflammation are absent. In this stage the process is specific for the disease and is reversible.

2. *The secondary retinal disease* arises from extension into the vitreous of protein-rich edema, neovascular tissue, and hemorrhage. An angiofibrous organization of the vitreous develops; this ultimately causes separation of the retina. A clinically apparent retrolental fibrous dentate membrane forms with retinal separation behind the lens.

In sections the uveal congestion disappears with retinal separation but some nonspecific inflammatory reactions appear. The later phases of the secondary state are not specific for the retinopathy of prematurity and represent the complication of separated retina arising from a rapid organization of the vitreous.

3. *The third state is that of pathologic repair and atrophy.* The microscopic findings are variable and also nonspecific. The following findings are common—completely separated gliosed and fibrotic retina, old hemorrhages, pigment disseminations, cholesterin and mineral deposits.

Glaucoma is often noted clinically as a sequence of shallowing of the anterior chamber and angle block. The late atrophic changes cause a shrunken globe.

Extraocular postmortem material may or may not show neovascular tissue. Orbital neovascular tissue is not characteristically found. Demonstrable involvements of the central nervous system, except structural and vascular prematurity, are not a usual finding.

243 Charles Street (14).

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RETROLENTAL FIBROPLASIA*

Evaluation of several changes in dietary supplements of premature infants with respect to the incidence of the disease

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The possibility that diet may be a factor in the development of retrolental fibroplasia in premature infants was first suggested by Terry[1] who called attention to the similarity of appearance of the eyes in this disease and that of the eyes of offspring of female rats deficient in vitamin A.[2]

While both clinical[3] and experimental[4] investigations now indicate that retrolental fibroplasia does not result from vitamin-A deficiency in either the mother or infant, recent data still suggest that its cause may be associated with nutrition.

Kinsey and Zacharias[5] presented evidence that the disease is becoming more prevalent and suggested that some environmental factor acting on the infant after birth may be responsible. In the present investigation an attempt has been made to correlate the incidence of various stages of retrolental fibroplasia with several changes in dietary supplements of premature infants.

The earlier studies[6] showed that the incidence of retrolental fibroplasia progressing to the stage of membrane formation in premature infants weighing between three and four pounds (1,360 to 1,820 gm.) at birth correlated positively with the use of a water-miscible multiple vitamin preparation, the quantity of iron fed, and, to a lesser extent, the amount of oxygen administered. While correlation between rise in incidence of the

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† From the Kresge Eye Institute.

disease and change in amount of dietary supplements given was not thought to constitute proof of any causal relation, it did suggest that the medication used might be responsible for the development of retrolental fibroplasia.

In an effort to determine whether any constituents of the water-miscible vitamin preparation, or iron, were responsible for producing retrolental fibroplasia, these supplements were omitted from the diet of premature infants. One of the purposes of this paper is to report the results of this experiment.

While the aforementioned study was in progress, Owens and Owens[6] reported that retrolental fibroplasia was arrested in some instances as a result of giving dl-alpha-tocopherol acetate therapeutically at the time the eyes showed signs of early stages of the disease, and that the incidence was reduced following the use of dl-alpha-tocopherol acetate prophylactically; that is, from birth.

The promising nature of this form of treatment stimulated the authors to attempt to repeat the Owenses' investigation. Accordingly, the effect on the course and incidence of retrolental fibroplasia of administering dl-alpha-tocopherol acetate therapeutically or prophylactically to all the infants born at the Boston Lying-in Hospital weighing four pounds or less at birth was determined. The second purpose of this paper is to report the results of this experiment.*

One hundred and 42 infants representing consecutive survivals to the age of three months or more were observed during the period of these investigations (January 1, 1948, through June 30, 1950).

Effect of withdrawal of water-miscible multiple vitamin preparation

To determine whether any of the constituents of the water-miscible multiple vitamin preparation* might have been responsible for the observed increase in incidence of retrolental fibroplasia, it would have been desirable ideally not only to withdraw the preparation entirely but to give no vitamin supplements in any form. However, because the need for additional vitamins in the diet of the premature infant had been amply demonstrated, it was thought inadvisable to eliminate all of the vitamin supplements contained in the preparation.

The possibility that a particular solvent or solubilizing agent might have been the constituent in the vitamin preparation responsible for the increased incidence of retrolental fibroplasia is believed to be eliminated by the observation that the incidence did not change significantly during a period in which different solvents and/or solubilizing agents were used.

The effect of withdrawal of the water-miscible multiple vitamin preparation was tested by altering the dietary regimen of premature infants in two ways. The first change in the use of vitamin supplements was instituted during the period January 1, 1948, through December 31, 1948.

It consisted in substituting vitamin D in water-miscible form, "B vitamins," and vitamin C in aqueous solution for the vitamin preparation given during the previous five years. The dosages of the vitamin supplements were equivalent to those given in the multiple vitamin preparation during 1947.

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* Since the completion of this study, La Motte,[7] in a lecture presented before the College of Physicians of Philadelphia, Section on Ophthalmology, reported on the failure of the prophylactic administration of vitamin E to prevent the development of the disease. The number of cases involved is not recorded in the Society Proceedings.

Reese and Blodi[8] reported that retrolental fibroplasia occurred with the same frequency in two series of cases, one treated with vitamin E and the other untreated. No figures were given regarding the number of infants involved in their study, or the percentage of retrolental fibroplasia in either group. They do cite an instance of identical twins in which one infant received vitamin E and developed retrolental fibroplasia; whereas, the other infant remained normal without vitamin E.

* Vi-Penta (Hoffmann-LaRoche Inc.).

The diet was not supplemented with vitamin A.

While the design of the experiment would have been improved by eliminating supplementary vitamin D as well, it was believed that the risk of developing rickets was too great. The latter vitamin was administered in water-miscible form rather than in oil to reduce the probability that the infants would contract lipoid pneumonia. Iron, in the form of ferrous sulfate, was continued in the dosage used previously.

The second change in the use of vitamin supplements (January 1 through August 31, 1949) consisted in eliminating "B vitamins" and iron from the supplements given during the previous period. Only vitamins D and C—both in a single water-miscible preparation*—were given routinely to the infants during this period. In those instances in which eyes showed early signs of retrolental fibroplasia dl-alpha-tocopherol acetate was also given.

The incidence of retrolental fibroplasia during the periods in which these two dietary regimens were employed, and the average incidence during the previous five years are shown in Table 1.† The over-all incidence of the disease has not changed significantly despite withdrawal of the water-miscible multiple vitamin preparation (Vi-Penta), or withdrawal of either vitamin A alone, or vitamin A, "B vitamins," and iron.

The zero incidence found for infants weighing three pounds or less at birth during 1949 is of doubtful significance. The possible effect of the therapeutic administration of dl-alpha-tocopherol acetate on the incidence of retrolental fibroplasia during this period will be discussed in the following section.

TABLE 1

INCIDENCE OF RETROLENTAL FIBROPLASIA (1948 TO SEPTEMBER 1949) IN PREMATURE INFANTS FOLLOWING OMISSION OF WATER-MISCIBLE MULTIPLE VITAMIN PREPARATION AND IRON FROM THE DIETARY SUPPLEMENT COMPARED WITH THE INCIDENCE DURING THE PREVIOUS FIVE YEARS

Year	Birth Weight		Total infants
	3 lbs.	3–4 lbs.	
	% Incidence	% Incidence	% Incidence
1948	25 (2/8)*	18 (6/33)	20 (8/41)
1949†	0 (0/12)	15 (5/34)	11 (5/46)
Av. 1943–1947	26 (10/38)	20 (33/163)	21 (43/201)

* Figures in parentheses represent number of infants.
† January 1 to September 1, 1949, includes infants treated therapeutically with dl-alpha-tocopherol acetate.

Effect of administration of dl-alpha-tocopherol acetate

dl-Alpha-tocopherol acetate was employed as a therapeutic agent for retrolental fibroplasia from January 1 through August 31, 1949, and as a prophylactic agent from September 1, 1949, through June 30, 1950. During these periods the eyes of premature infants were examined ophthalmoscopically at approximately weekly intervals in the hospital nursery, and at approximately biweekly intervals after discharge from the nursery.

Infants whose eyes remained normal were examined routinely until they were at least three months of age, and infants whose eyes showed signs of retrolental fibroplasia were examined until they were six months of age or more, depending on the ocular condition.

* Especially prepared and kindly supplied by U. S. Vitamin Corporation, New York.

† The figures in the table are based on cases of retrolental fibroplasia in which membranes were present in one or both eyes.

dl-Alpha-tocopherol acetate was employed therapeutically when the first manifestations of the disease were observed—that is, enlargement of arteries and veins, with some tortuosity (stage 2 in the following classification). The compound was employed prophylactically starting a few days after birth. The plasma level of vitamin E was determined each time the infant was examined to obtain some indication of the extent to which absorption took place*

To facilitate comparison of the condition of one infant's eyes with that of another, and to follow more readily the course of the disease, an arbitrary numerical classification of the stages in the development of the disease was devised.

Numerical classification of stages in the development of retrolental fibroplasia

Stage 0—Normal.

Stage 1—Enlarged arteries and veins—relatively straight.

Stage 2—Greater dilatation with tortuosity.

Stage 3—Stage 2 plus generalized retinal edema with some hemorrhage and/or vitreous haze.

Stage 4—Stage 3 plus hemorrhage into vitreous and/or localized retinal detachment.

Stage 5—Stage 4 plus disturbance in disc margins from retinal fold or partial peripheral or central membrane formation.

Stage 6—Partial to complete occlusion of pupil by membrane.

TABLE 2

Outcome of acute manifestations of retrolental fibroplasia in infants given dl-alpha-tocopherol acetate therapeutically or prophylactically

	No. of Infants	Stages of Retrolental Fibroplasia						Incidence of Severe Form
		0–1	2	3–4		5–6		
				Acute	Terminal	Acute	Terminal	
Jan.–Sept. 1949 dl-α-tocopherol acetate therapeutically	46	25	13	3	1	5*	5	11% (5/46)
Sept. 1949–July 1950 dl-α-tocopherol acetate prophylactically	55†	28	9	19‡	2	3§	3	5% (3/55)

* One infant (both eyes affected) of a pair of twins received no dl-alpha-tocopherol acetate.

† The figure for the total number of infants (55) does not represent the sum of the four groups because in four infants the two eyes were classified differently.

‡ Two infants received blood transfusions and cortisone as well as dl-alpha-tocopherol acetate.

§ One infant received blood transfusions and ACTH as well as dl-alpha-tocopherol acetate.

Therapeutic use of dl-alpha-tocopherol acetate

Of the 46 premature infants who were studied from January 1, 1949, through August 31, 1949, 21 infants were given dl-alpha-tocopherol acetate therapeutically in divided doses ranging from 30 to 150 mg. a day. To serve as a control one infant of a pair of twins, both of whom developed signs of retrolental fibroplasia, was not given dl-alpha-tocopherol acetate. Both of these twins, and three other infants, continued to develop retrolental fibroplasia to stages at which membrane formation was observable (stages 5 and 6).

Three other infants developed the disease to stages at which there was generalized re-

* Blood was drawn by heel puncture and vitamin E levels were determined by the micromethod of Quaife and others.[9] The average plasma level of vitamin E in 29 infants during the first two weeks after birth whose diets were not supplemented with dl-alpha-tocopherol was 0.6 mg. percent.

tinal edema and localized detachment (stages 3 and 4). The pathologic condition of the eyes of two of these infants disappeared at a later date.

The incidence of retrolental fibroplasia at Stages 5 and 6 during this period when dl-alpha-tocopherol acetate was given therapeutically was 11 percent, a value which is not thought to be significantly lower* than that of the previous year (20 percent) when dl-alpha-tocopherol acetate was not given. The results are presented in line 1 of Table 2.

In all instances administration of dl-alpha-tocopherol acetate maintained the plasma levels at or higher than one mg. percent, a value which is more than double that of infants who were not supplemented and whose eyes remained normal.

That the course as well as the severity of the disease was uninfluenced by the therapeutic use of dl-alpha-tocopherol acetate can be illustrated graphically by plotting the numerical stages of the disease as a function of the age of the infant. For example, in the case of the twins, one of whom received dl-alpha-tocopherol acetate (fig. 1) and one of whom did not (fig. 2), the rate of progression as well as the extent of the disease was approximately the same. The plasma level of vitamin E is shown by the broken line of the graph.

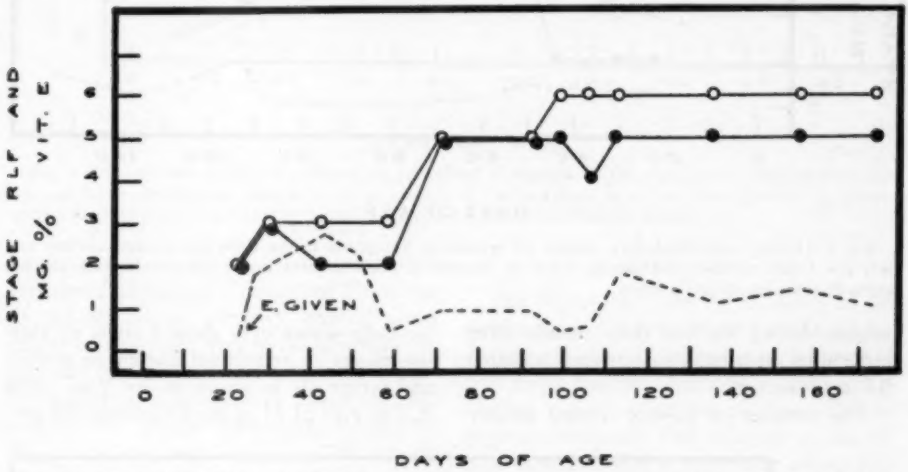

Fig. 1 (Kinsey and Chisholm). Stages of retrolental fibroplasia in the right eye (closed circles) and left eye (open circles), and plasma levels of vitamin E (broken line) in one of a pair of twins who was given dl-alpha-tocopherol acetate therapeutically.

Prophylactic use of dl-alpha-tocopherol acetate

From September 1, 1949, through June 30, 1950, 55 premature infants were given 50 mg. of dl-alpha-tocopherol acetate prophylactically three times a day, in addition to the basic vitamin supplement used in the preceding test period—namely, vitamins D and C.

The average plasma level of vitamin E in these infants was approximately four mg. percent, although the levels during the first three months after birth varied between one and 10 mg. percent in different infants and at different times. The average plasma level of vitamin E in unsupplemented premature

* A decrease in incidence of this magnitude might be expected to occur 15 times out of 100 by chance.

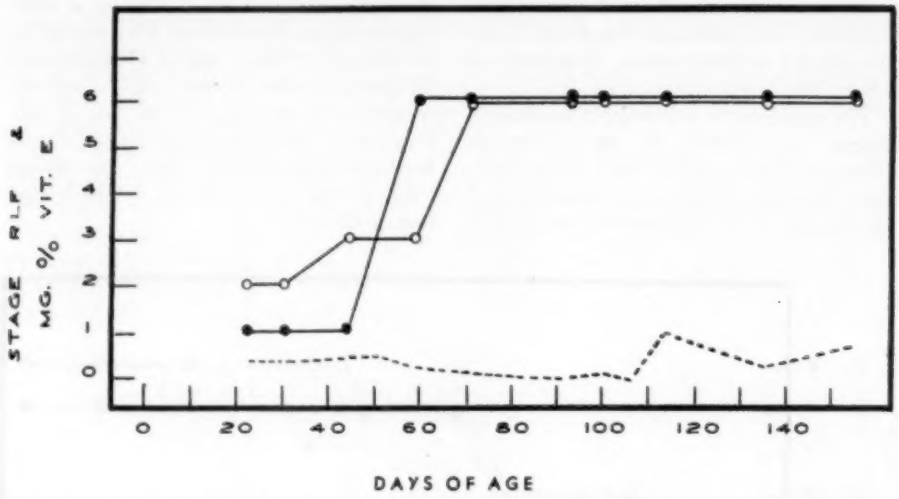

Fig. 2 (Kinsey and Chisholm). Stages of retrolental fibroplasia in the right eye (closed circles) and left eye (open circles), and plasma levels of vitamin E (broken line) in the other twin who was not given dl-alpha-tocopherol acetate.

infants during the first three months after birth in the previous year was approximately 0.5 mg. percent.

The number of infants treated prophylactically whose eyes showed signs of various stages of retrolental fibroplasia acutely and terminally is shown in line 2 of Table 2. The eyes of 31 of the 55 infants (56 per-

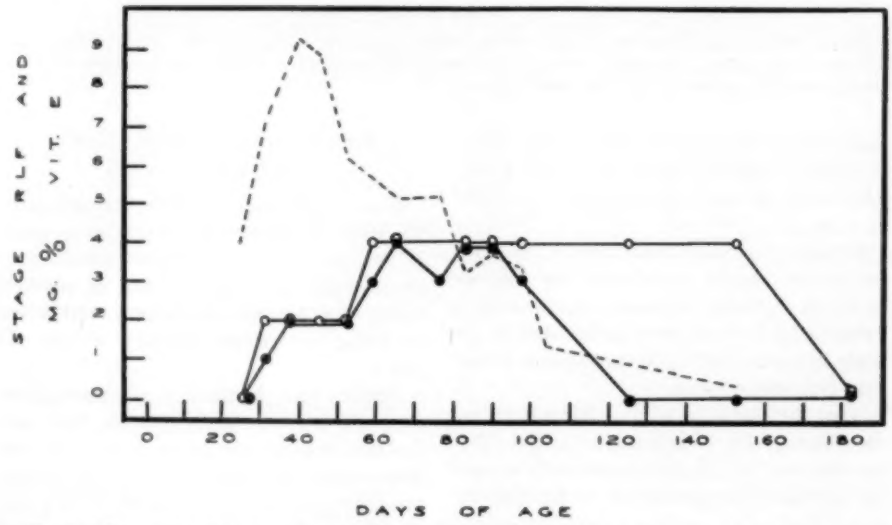

Fig. 3 (Kinsey and Chisholm). Stages of retrolental fibroplasia in the right eye (closed circles) and left eye (open circles) and plasma levels of vitamin E (broken line) in a case given dl-alpha-tocopherol acetate prophylactically in which both eyes returned to normal.

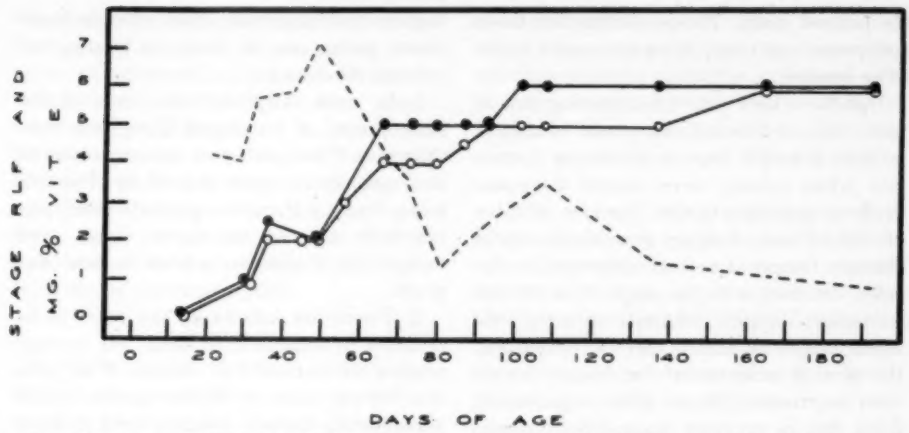

Fig. 4 (Kinsey and Chisholm). Stages of retrolental fibroplasia in the right eye (closed circles) and left eye (open circles) and plasma levels of vitamin E (broken line) in a case given dl-alpha-tocopherol acetate prophylactically in which both eyes developed the severe form of the disease.

cent) showed some acute manifestations of retrolental fibroplasia. The eyes of five of the 55 infants (nine percent) showed some visible residue after they were six months of age, and the eyes of three infants (five percent) developed membranes bilaterally. No residue was visible ophthalmoscopically in the eyes of the remainder of the 31 infants who showed some acute manifestations of retrolental fibroplasia.

An illustration of the course of the disease in one of the cases in which regression of the acute manifestations occurred is shown in Figure 3. The course of the disease in the eyes of one of the infants given dl-alpha-tocopherol acetate prophylactically which progressed to membrane formation bilaterally is illustrated in Figure 4. The rate of progression of the disease is typical and does not appear to have been influenced by high plasma levels of vitamin E.

The variation in incidence of retrolental fibroplasia at the Boston Lying-in Hospital during the period 1938 through June, 1950, is shown in Figure 5. The arrows at points A, B, and C of the graph represent the times at which the three changes in dietary regimen of the premature infant were instituted.

Discussion

The observation that the incidence of the severe form of retrolental fibroplasia did not change significantly following withdrawal of the water-miscible multiple vitamin preparation suggests that the rise in incidence between 1943 and 1948 was not caused by Vi-Penta. Conclusive proof that vitamins D and C are without effect on the incidence has not been obtained because they were still administered in a water-miscible menstrum during the period encompassed by

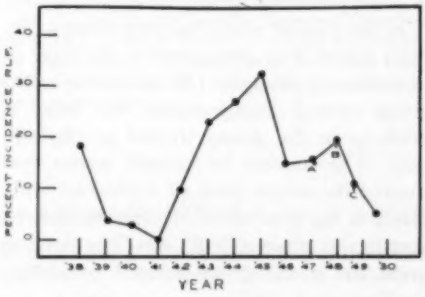

Fig. 5 (Kinsey and Chisholm). The incidence of retrolental fibroplasia in premature infants weighing less than four pounds at birth at the Boston Lying-in Hospital. The arrows at points A, B, and C represent the time at which the three different dietary regimens were altered (see text).

the present study. The possibility that these substances are toxic, however, seems to us to be remote.

Data have been presented showing that in some cases retrolental fibroplasia continued to develop to the stage of membrane formation when infants were treated therapeutically or prophylactically. The eyes of three of five infants showing generalized retinal changes (stages 3 and 4) continued to develop the disease to the stage of membrane formation despite administration of dl-alpha-tocopherol acetate therapeutically, and the over-all incidence of the disease in children so treated did not differ significantly from that in previous years. We conclude, therefore, that therapeutic administration of dl-alpha-tocopherol acetate is without value.

Generalized retinal changes were observed in the eyes of 22 of the 55 infants receiving dl-alpha-tocopherol acetate prophylactically. Hence it may be concluded that the prophylactic use of this compound does not reduce the incidence of early ocular changes associated with retrolental fibroplasia.

This conclusion agrees with that presented previously by Owens and Owens.[10] However, these workers reported that the percentage of eyes which went on to develop complete retrolental membranes in a group not given dl-alpha-tocopherol acetate prophylactically was three times as great as in a supplemented group.

In the present study the proportion of infants whose eyes progressed to the stage of membrane formation (11 percent) in the group treated therapeutically was twice as great as in the group treated prophylactically. The number of infants whose eyes showed the severe form of retrolental fibroplasia in the year before dl-alpha-tocopherol acetate was given (1948) was four times as great as in the group treated prophylactically.

These figures are similar to those of Owens and Owens but they are not statistically significant because of the variability in incidence from year to year.

The following observations seem to us to weaken the argument that dl-alpha-tocopherol acetate may be useful in treating retrolental fibroplasia.

1. In some hospitals[11] no cases of the severe form of retrolental fibroplasia were observed. The number of infants involved was sufficiently great that these hospitals were, from a statistical point-of-view, significantly free of the severe form even though no dl-alpha-tocopherol acetate was given.

2. Premature infants do not seem to be deficient in vitamin E at birth; the average plasma concentration of vitamin E at birth was 0.6 mg. percent. Neither do the infants subsequently become deficient even in those instances when no supplementary dl-alpha-tocopherol acetate is administered as evidenced by an average plasma concentration of 0.5 mg. percent of vitamin E during the first three months of life.

3. We have not observed any correlation between the plasma levels of vitamin E during the first few weeks of life and the incidence of retrolental fibroplasia. Thus, it would appear that much of the rationale for the use of dl-alpha-tocopherol acetate as a preventive measure for retrolental fibroplasia is invalid. In so far as it may be of value in preventing the more severe form of the disease, it must act pharmacologically rather than as a vitamin. Indeed, Owens and Owens have expressed this point of view.

While the possibility that dl-alpha-tocopherol acetate may be an effective pharmacologic agent for retrolental fibroplasia may seem remote in view of the foregoing observations, nevertheless, because of the seriousness of the disease, the lack of any other form of prophylaxis, and the fact that administration of dl-alpha-tocopherol acetate produced no noticeable toxic manifestations, we believe that more data should be accumulated concerning its effectiveness in preventing retrolental fibroplasia before its real value can be assessed.

The observation that, in a considerable proportion of cases of retrolental fibroplasia, the disease regressed from Stage 3 or 4 and

the eyes became normal suggests that caution should be used in evaluating other forms of treatment, such as ACTH or cortisone, when administered at these stages; caution should also be used in dealing with parents who may have become aware that their infants have developed early signs of retrolental fibroplasia, since the prognosis at these stages, particularly when dl-alpha-tocopherol acetate is administered prophylactically, is reasonably good.

Summary

1. Withdrawal of the water-miscible multiple vitamin preparation and iron used as supplements to the diet of premature infants born at the Boston Lying-in Hospital weighing less than four pounds at birth and substitution of only vitamins D and C in water-miscible form were without apparent effect on the incidence of retrolental fibroplasia.

2. Administration of dl-alpha-tocopherol acetate therapeutically in daily doses ranging from 30 to 150 mg. to premature infants at the time the eyes showed vascular changes characteristic of the early stages of retrolental fibroplasia did not reduce the incidence of the severe form of the disease significantly.

3. Fifty-six percent of the premature infants given 50 mg. of dl-alpha-tocopherol acetate prophylactically from birth three times a day developed vascular changes, and 40 percent also developed vitreous and retinal changes associated with retrolental fibroplasia.

4. Five percent of the infants given dl-alpha-tocopherol acetate from birth developed the severe form of the disease involving membrane formation, compared with 11 percent who did not receive dl-alpha-tocopherol acetate prophylactically. This difference in incidence is of doubtful significance.

5. The average plasma level of vitamin E in infants at birth unsupplemented with dl-alpha-tocopherol acetate was found to be 0.6 mg. percent, suggesting that premature infants are not characteristically deficient in vitamin E. No correlation was observed between the plasma level of vitamin E in the premature infant and the incidence of retrolental fibroplasia.

6. The large proportion of eyes which recover, apparently spontaneously, from stages of retrolental fibroplasia involving retinal as well as vascular changes suggests the need for caution in evaluating possible forms of therapy.

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Acknowledgment

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Dr. Paul Goldhaber made duplicate analyses for vitamin E on more than 1,000 samples of plasma from infants followed during this study.

Dr. Clement Smith and Dr. Stewart Clifford of the Boston Lying-in Hospital assisted in planning the experiments; Dr. Earl Seale performed many of the ophthalmoscopic examinations on infants in the hospital nursery.

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HUMAN GALACTOSEMIA CATARACT*

Report of a case

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Six infants representing almost half of the reported cases of galactosemia in human beings have had cataracts.[1-4] The incidence is probably higher since many of the reports did not mention an ocular examination.

Galactosemia[1, 2-12] is apparently a congenital anomaly, usually making its appearance within the first few months of life. The findings may be summarized as hepatomegaly, galactosuria, galactosemia with impaired galactose tolerance, loss of and failure to gain weight (in spite of voracious appetite), lethargy, mental dullness, absence of interest in surroundings, cataracts, albuminuria without impairment of renal excretory function, and secondary anemia.

Galactose is part of the lactose molecule in milk. The disease is apparently due to a decreased ability of the liver to convert galactose into the more utilizable glucose. Bruck and Rapoport[4] feel that galactose in increased concentrations is specifically toxic to the various involved tissues. Pathologic reports by several authors[13] have revealed that the changes are identical with those seen in simple starvation.

The treatment of this disease is to provide a galactose-free diet and, if this is done relatively early, the changes already enumerated are clinically reversible. Response is often dramatic. The galactose intolerance, however, would seem to be permanent.

Of the six previously reported cases with cataracts, two had complete clinical recovery of the cataracts, two had marked regression, and in two discissions were required.

There have been many investigations with experimental animals to produce and study cataracts caused by diets with a high lactose or galactose content.[14-31] Rats on a diet containing 25- to 50-percent galactose or 70-percent lactose as all or part of their carbohydrate quite consistently developed lens opacities.

The time of onset of these opacities was proportional to the amount of galactose ingested. Younger rats tended to show earlier nuclear involvement.[16]

As a rule, the ophthalmoscopic findings were peripheral equatorial cortical "snowflake" opacities which subsequently coalesced into vacuoles. These gradually spread anteriorly to a complete superficial opacity.[26] At this time, slitlamp examination reveals numerous punctate and striate opacities in the cortex. Others have emphasized a rapid and early appearance of senile suture lines.[9] The cataract then progresses to maturity.

Dodge[15] states that often an early finding is a perinuclear opacity appearing as a halo or line of sclerosis around the nucleus. Later this becomes more dense and a true nuclear cataract frequently develops.

If the diet is normalized when the cataract

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is immature, it will completely regress ophthalmoscopically.[16] There remains, however, permanent histologic evidence of degeneration.[22] Mature cataracts, on the other hand, regress with remaining nuclear opacity. Detailed histologic studies have been described.[15, 22]

Salit, Swan, and Paul[25] have shown that the mineral composition of these cataracts is similar to those of senile cataracts. Bellows and Chin[24] believe that the cataract is due to hypertonicity and osmotic imbalance. There is evidence that galactose is toxic to the capsular epithelium.[14, 18] Bellows[19] further states that galactose is toxic to lenticular tissue because it produces a disturbance of the internal oxidative mechanism.

Even before the appearance of visible opacities the cysteine and glutathione content of these lenses is found to be significantly reduced. The addition of cysteine, vitamin C, or yeast (glutathione) to the galactose diet will slow the cataract formation.[19]

Yudkin and Arnold[16] believe that calcium infiltration is secondary to lens tissue degeneration.

Case report

History. R. S., a six weeks' old white male infant, was admitted to the University of Kansas Medical Center on March 25, 1950. A diagnosis of congenital galactosemia was established. A detailed study of this case will be reported by the Department of Pediatrics of the University of Kansas Medical Center.

Physical examination. The positive findings are summarized as follows: weight, 2,275 gm.; protuberant abdomen with distended veins; liver, three cm. below the costal margin; milky yellow abdominal fluid with a specific gravity of 1.010 and protein of 1.7 gm. percent; peripheral edema; four-plus glycosuria which proved to be galactose; one-plus albuminuria; 3,440,000 R.B.C., with 67 percent hemoglobin, 19,950 W.B.C.; blood sugar, 160 mg. per cent (micro. method); total protein, 4.20 gm.; albumin, 3.18; globulin, 1.02; normal glucose tolerance and reduced galactose tolerance.

The ocular examination on April 7, 1950, revealed the following: External examination was normal. The eyes were straight except for apparent large angle kappas. Ductions and versions were normal. The corneas were clear. The anterior chambers were of normal depth and clear. The pupils were round, equal, and reacted well to light.

Ophthalmoscopy revealed a moderately dense homogeneous opacity of the nuclear areas in both lenses. There were also occasional small equatorial cortical vacuoles.

Slitlamp examination revealed an area of diffuse homogeneous relucency entirely throughout the fetal and embryonal nuclei with a few scattered small brilliant white opacities. The cortical area seemed optically clear. There was no apparent fundus pathology.

During the following six weeks, with the child on a galactose-free diet, periodic examination revealed a slight clearing of the nuclear haze.

At the age of seven months, the child fixed and followed objects very well. The cortical opacities had completely disappeared and, using reduced illumination with the ophthalmoscope, only faint nuclear or perinuclear haziness was present. Slitlamp examination was unsatisfactory because of the child's markedly increased activity.

Summary

The findings in galactosemia of human beings are summarized.

Galactose cataracts in experimental animals are discussed.

The seventh case of human galactosemia with cataracts is presented.

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Ophthalmic Miniature

A very long-legged white spider rubbed up with oil removes white spots from the eye if assiduously used; therefore mind and rub a good many with sufficient oil lest the medicine be exhausted before the cure is complete.

Marcellus Empiricus of Bordeaux,
De medicamentis empiricis (circa 385 A.D.)

GALACTOSEMIA CATARACT*

Report of a case

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Galactosemia is of considerable importance to the ophthalmologist in view of the well-recognized toxic and cataractogenic effect of the monosaccharide in experimental animals. Galactosemia, in the human, is an extremely rare congenital anomaly of carbohydrate metabolism.

The essential features of this clinical entity are: hepatomegaly, splenomegaly, galactosuria, albuminuria, diarrhea, vomiting, failure to gain weight or to grow, and development of cataracts. Occasionally secondary features of the syndrome may be seen, such as icterus, anemia, osteoporosis, lethargy, and absence of the tendon reflexes.

The development of either nuclear or zonular lenticular opacification has been observed in nearly half of the reported cases of galactosemia. The removal of galactose from the diet results in improvement of all the signs and symptoms of the disease. It is of interest that the opacification of the lens may partially or completely disappear, providing dietetic treatment is initiated before irreversible cataractous formation has developed.

It is the purpose of this paper to report the occurrence of galactosemia in a white infant, a girl, aged eight weeks.

Literature

It may be conservatively estimated that less than 12 cases of authenticated galactosemia are available for study in the literature.

Most authors feel that the first accepted case of galactosemia was reported by F. Göppert[1] in 1917. The patient was two years and five months of age when first observed. Two siblings of this child had died early in life presenting icterus and enlarged livers. A third sibling, who survived, also had hepatomegaly. Göppert made no statement concerning the eyes of the children.

In 1908, Von Reuss[2] reported galactosuria in an eight months' old infant who presented cirrhosis of the liver at autopsy. This author believed that this was a case of alcoholic cirrhosis, since the child had been fed tea and cognac daily since four months of age.

G. Fanconi,[3] in 1933, reported an affected child, the second youngest of 12 siblings. Two of these siblings had zonular cataracts. The reported patient was found to have had bilateral zonular cataract requiring surgical interference. It is interesting to note that the parents of the above sibship were first cousins. Neurofibromatosis was described in the patient, one sibling, and the mother.

Mason and Turner,[4] in 1935, recorded chronic galactosemia in a Negro male child, the youngest of seven children. Cataracts are not mentioned in the original report, but were admitted in a personal communication to Bruck and Rapoport.

Norman and Fashena[5] (1943) reported chronic hypergalactosemia in a white male infant of 11 weeks. No ocular pathology was described.

Mellinkoff and his collaborators[6] (1945) published a typical case of galactosemia in a two months' old white male. The ocular findings were carefully enumerated. They stated: "The lens presented a sharp zone of demarcation in that the nucleus was more

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highly refractile; there was no actual opacity, however." When milk was removed from the patient's diet all pathologic symptoms and signs disappeared, including the lens changes.

Goldbloom and Brickman[7] reported two cases of galactosemia in 1946. The first case, a six months' old male, presented in addition to the usual signs and symptoms, bilateral dense central lenticular opacification. The cataract became less dense with the passage of time, but surgery was necessary at the age of six and one-half years. The second case, in a white girl, aged three and one-half months, also exhibited "bilateral pinpoint cataracts." The authors felt that the cataracts had regressed somewhat when the child was seen at the age of nine and one-half months.

Goldstein and Ennis[8] (1948) reported galactosemia in a white male infant aged two and one-half months. They state "bilateral zonular cataracts were observed." When seen at six and one-half months of age, after treatment, the "cataracts had completely disappeared."

Greenman and Rathbun[8] reported an 18-week-old white male presenting bilateral nuclear cataracts, hepatomegaly, splenomegaly, and ascites. "Clinical improvement was evident almost immediately after the withdrawal of galactose from the diet. Only vestigial cataracts and moderate hepatomegaly were present four months afterwards."

Case report

L. B., a white female infant, was admitted to the pediatric ward of the University Hospital on August 8, 1949, at the age of eight weeks with a chief complaint of abdominal enlargement.

Family history. Both parents were 25 years of age and were in excellent health. The father was told he had had rheumatic fever at 19 years of age but he has been asymptomatic since. There were no siblings and no history of a similar disease occurring in any member of the family.

Present illness. The patient was born at term and the delivery was uncomplicated. The birth weight was eight pounds, four ounces. The child was discharged from the hospital at four days of age on alternate breast and formula Baker's milk feedings.

She did well until the seventh day of life when she began to vomit all or most of every feeding. She was taken off breast milk and several changes in the formula were made. At varying intervals evaporated milk, Alacta, and boiled skimmed milk formulas were tried without success.

Due to weight loss and dehydration she was admitted to the local hospital for parenteral fluid administration. The child was hospitalized for five days and was discharged on an evaporated milk formula. A severe diarrhea developed shortly after and it was observed that the abdomen was distended and "hard."

The patient was readmitted to the local hospital and a paracentesis was performed on August 5, 1949, with removal of 600 cc. of slightly cloudy fluid from the abdomen. In spite of therapy, diarrhea and vomiting continued. The patient was transferred to the University of Michigan Hospital on August 8, 1949.

Physical examination revealed an eight weeks' old infant who appeared malnourished and dehydrated. The abdomen was distended with fluid which was draining from the paracentesis wound. The liver edge was smooth and sharp and extended to the level of the umbilicus at the midclavicular line. The admission weight was nine pounds, three ounces. The remainder of the examination was not remarkable.

The child took an evaporated milk formula fairly well but vomited at frequent intervals. The diarrhea continued for several days after admission.

Laboratory findings. Urine. Repeated urinalysis revealed marked melaturia with qualitative Benedict's solution. This reducing substance was demonstrated to be galactose (negative yeast fermentation, typical osozone crystal formation, negative pentose tests). Albuminuria was present as were frequent granular casts.

Blood. Hemoglobin 8.5; R.B.C., 2,600,000; W.B.C., 13,200; prothrombin time (Quick) 100 percent of normal; blood urea nitrogen, 34.6 mg. percent (following hydration). Total protein, 4.4 gm.; albumin: globulin ratio, 2:1.

Glucose tolerance test (1.75 gm. glucose per Kg.):

	Total Blood Sugar
Fasting	35 mg.%
½ hour	46 mg.%
1 hour	97 mg.%
2 hours	103 mg.%
3 hours	74 mg.%

Galactose tolerance test (3.5 gm. galactose):

	Total Blood Sugar	Galactose Blood Sugar
Fasting	86 mg.%	—
½ hour	125 mg.%	—
1 hour	164 mg.%	69 mg.%
2 hours	218 mg.%	136 mg.%
3 hours	264 mg.%	—

After the diagnosis of galactose intolerance was established (at eight weeks of age, the youngest

reported), the patient was given a lactose- and galactose-free diet. This consisted of casec and nutramigen with added carbohydrate and water to approximate the protein and caloric content of an adequate evaporated milk formula. Within a week there was a marked reduction in ascites. The urine became sugar- and albumin-free and has remained so. Blood urea nitrogen one week after the new diet was initiated was 15.3 mg. percent. All gastrointestinal symptoms subsided.

Ophthalmologic examination. The patient was referred to the Department of Ophthalmology on August 19, 1949, as soon as the diagnosis of galactosemia was established.

The external examination showed no ocular pathologic condition. The funduscopic examination presented a sharply outlined zonular area of increased density of an opalescent nebular nature just beneath the capsule in both lenses. In addition it was evident that the nuclear areas were likewise somewhat opalescent in character.

The discs, vessels, and macular areas were normal in appearance bilaterally.

Comment

Galactosemia is an anomaly of carbohydrate metabolism in which the metabolism of galactose is impaired, resulting in an accumulation of this monosaccharide in the blood stream with the resultant excretion in the urine.

As mentioned by Goldstein and Ennis,[9] it appears that there is a mutual antagonism between the two sugars—galactose and glucose. In fact it has been questioned or hypothecated that excessive quantities of galactose may interfere with normal oxidation of glucose.

Since it is believed that the liver is the site of conversion of galactose to glucose we have, in the presence of galactosemia, indirect evidence of impaired liver function. The metabolic error may thus be a decreased rate of conversion of galactose to glucose, most likely an enzymatic want or defect.

The resultant accumulation of galactose in the blood stream produces toxic manifestations. It is strongly suggested that toxic manifestations—cataract, albuminuria, loss of tendon reflexes, and so forth—are due to the local presence of excessive galactose in the tissues.

D. B. Kirby[10] and his associates have capably demonstrated that galactose is directly toxic to lens tissue. Mitchell[11] and Dodge[13] revealed that cataract in experimental animals developed rapidly and consistently when the animals were fed diets containing galactose. Bellows and Chinn[14] suggested that galactose cataract is caused by the disturbances connected with the hyperglycemia and the resultant increased sugar content of the aqueous humor.

The above-mentioned and other similar animal experimentation has contributed much to our comprehension of the pathophysiology of galactosemia. Much remains to be learned and it is hoped to obtain liver biopsy tissue with which to conduct experimentation in an effort to ascertain the missing enzyme or faulty step in carbohydrate metabolism in these cases.

Galactosemia may well be an innate error of metabolism, most likely exhibiting a simple autosomal recessive mode of inheritance. The presence of consanguinity and the multiple occurrence of the disease in siblings gives weight to this hypothesis. The close relationship of galactosemia to the glycogen storage diseases such as von Gierke's, a recessive error of metabolism, would also suggest a hereditary basis.

The parents in our case were normal. The father is a member of a sibship of 14, all living and well. The mother is a member of a sibship of eight, one child of which died in infancy but without symptoms suggestive of galactosemia. The child herein reported has 21 normal first cousins.

The reported phenomenon of reversibility of the cataracts, as well as other signs of the disease, is interesting. It is our belief that, unless the diagnosis is established very early in the course of the disease and treatment initiated immediately, permanent lens damage will ensue.

Follow-up ophthalmic examination on October 21, 1949, revealed no specific change in the cataractous condition, but the funduscopic details were more clear and detailed. It appears, thus, that galactosemia (temporary and treated) produces no permanent or irreversible damage to the lens epithelium in that proliferation may resume and deposit

healthy clear cortex. With the growth of new lens material and the accumulation of new cortex the original cataractous change may seem to recede in size.

The reversibility of cataractous changes in animal experiments has been authoritatively observed.[12, 13]

Summary

A case of galactosemia, the youngest patient reported, is summarized. The interest of the ophthalmologist should be stimulated in this error of carbohydrate metabolism because of the association of cataract. These cataracts are zonular in character, although nuclear changes may also result.

The reversibility of symptoms and signs of galactosemia with initiation of dietary treatment make it important that the diagnosis be established as early as possible to avoid permanent tissue changes.

University Hospital.

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Ophthalmic Miniature

I had occasion to pass through Liége and to stay there for a time. There I performed six operations in accordance with this method, and all with the greatest success. One which I performed at Cologne on a priest of a religious order yielded a very surprising result, inasmuch as the cataract was as soft as jelly. In spite of that fact, the priest was able, fourteen days later, to read the Mass.

Jacques Daviel,

Sur une nouvelle method de guérir la cataracte par l'extraction du cristallin, Mém. Acad. roy. de chir., II: 337, 1753.

TREATMENT OF RETINOBLASTOMA BY DIATHERMIC COAGULATION*

Report of a case

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New York

Retinoblastoma, formerly known as retinal glioma, is a malignant tumor of infancy and childhood, with a fatal outcome from invasion of the brain and widespread metastases. Treatment consists in removal or destruction of the tumor before it spreads.

When the disease is monocular, enucleation of the involved eye and of the orbital portion of the optic nerve is indicated. When the growth is present in both eyes, the more extensively affected eyeball must be removed together with a segment of the optic nerve.

The treatment of the second eye depends upon the size and extent of contained tumor and the possibility of useful vision. Enucleation of the second globe is necessary if the growth is large. If the neoplasm in the less involved eyeball is small, the possibility of destroying the growth by radiation or by diathermy must be thoughtfully considered.

Martin and Reese[1] have published the results of their successful treatment of retinoblastoma by the fractionated or divided-dose principle of roentgen radiation. This method is most applicable to a tumor which is situated behind the equator of the globe.

The destruction of the tumor in the second eye may also be accomplished by the use of diathermic coagulation. This method was first reported by Weve[2] in 1932. His first case revealed complete destruction of the growth as shown by microscopic studies of the globe which was later removed because of the fear of recurrence.[3]

In 1935, the same author[4] presented a child, aged two-and one-half years, with two small "gliomas" in the remaining eye, the other having been destroyed by a neglected tumor. The two growths were eradicated by diathermy, leaving scars hardly larger than the original tumors, and with good vision remaining.

In a paper on the operative treatment of intraocular tumors, published in 1937, Weve[5] mentioned an earlier case of retinoblastoma, treated by diathermy, with later recurrence necessitating enucleation. In his Bowman Lecture, delivered in 1939, he[6] stated that he had tried diathermy several times for the treatment of retinoblastoma, but could not prevent later recurrences. He therefore did "not dare to apply this technique except in cases where excision is absolutely refused by the parents or where a single and very early tumor is found in the only good eye."

In a recent letter[3] to me, Weve has become more optimistic, for he writes: "But since then I have got much more experience and I have now had for years under observation some cases of glioma that have done exceedingly well after diathermic treatment, one of them with no less than three big tumours. The latest case is actually still in my hospital (a single rather big tumour in the only eye, the other being already extirpated). Dr. François from Lille, France, sent me last year a case that he had operated in the same way with rather good success, although there was still some tumour left in the centre of the field of coagulation. In this case I actually extirpated what was left of the tumour and could examine it anatomically. As far as I know, the case healed nicely."

In 1944, de Roetth[7] reported on two pa-

* From the Department of Ophthalmology, Columbia University, College of Physicians and Surgeons, and the Institute of Ophthalmology of Presbyterian Hospital. Presented before the Section on Ophthalmology of the New York Academy of Medicine, February, 1951.

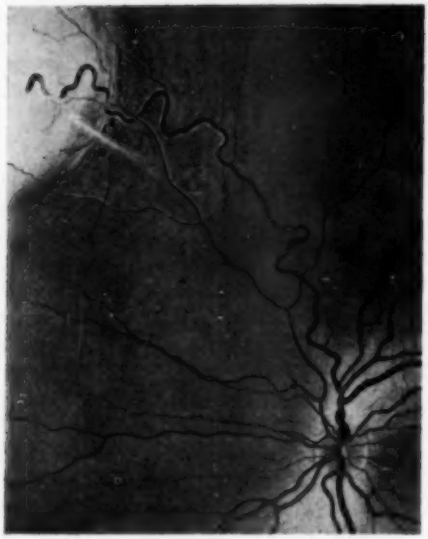

Fig. 1 (Perera). Photograph of drawing of background of left eye, showing tumor in upper nasal quadrant.

tients treated in the State Eye Hospital in Budapest. The electrode was introduced through the sclera 55 times for two to three seconds each time, using 50 to 60 milliamperes. In one case the tumor was arrested for a few months but then showed progressive growth. In the other instance the tumor, which measured 2.5 by 3.5 disc diameters, was arrested and apparently destroyed. In the latter patient, the growth became calcified and had not changed in appearance for 18 months after operation.

Weve[5] presented an interesting case before the Netherlands Ophthalmological Society in 1947. The patient, a girl, aged eight months, was the daughter of a man both of whose eyes had been removed for retinoblastoma in early childhood. The girl's right eye was enucleated, and the diagnosis of retinoblastoma confirmed by pathologic examination. One year later, a small round pinkish tumor was found in the left eye near the ora serrata in the 3-o'clock meridian. The growth measured three or four disc diameters, The child was referred to Professor Weve, who performed a surface diathermic coagulation. The tumor became yellowish-white and the adjacent retina bluish-white. The scar showed a surrounding zone of pigment.

Report of case

History. R. C., a seven-year-old white boy, referred to me by Dr. Philip Cohen, was first seen on October 30, 1948, with the complaint of an inflamed right eye for two weeks. The parents of the boy stated that this eye has been "slightly crossed" since early childhood. He had suffered from a mild attack of measles in June, 1948.

The family history was noncontributory. A younger brother was healthy.

Ocular examination by my associate, Dr. Edward J. Bassen, and me showed a blind right eye containing a slightly shallow anterior chamber, a clear lens, and a completely detached retina, which was yellowish in color and included pale areas. Transillumination was irregularly impaired.

The left eye had a visual acuity of 20/20. The interior of this eye revealed clear media, sheathed and dilated retinal vessels in the upper nasal quadrant, and a grayish area of elevated retina between the equator and the ora serrata superonasally (fig. 1).

This lesion contained white areas and did not extend to the ora serrata, as revealed by careful ophthalmoscopic study with indentation of the sclera. The dilated and tortuous superior nasal vein of the retina issued from the tumor mass. The clinical diagnosis of bilateral retinoblastoma was made.

The boy was admitted to the Institute of Ophthalmology of Presbyterian Hospital, where he was examined by Dr. J. H. Dunnington and Dr. A. B. Reese. Both agreed with the diagnosis of retinoblastoma.

A complete physical examination and skeletal X-ray studies showed no evidence of metastases. Enucleation of the right eyeball with implantation of a gold sphere into Tenon's capsule was performed on Novem-

ber 1, 1948. Healing was uneventful. Pathologic examination of the removed globe showed retinoblastoma (figs. 2 and 3). The optic nerve behind the eyeball was not invaded by tumor.

By November 16, 1948, it was evident that the lesion within the left eye had increased slightly in size. Dr. Reese and I considered three possible forms of treatment: (1) Enucleation, (2) radiation, and (3) diathermic coagulation.

The first considered treatment was set aside as too radical, since there was a reasonable chance to destroy the tumor. Radiation

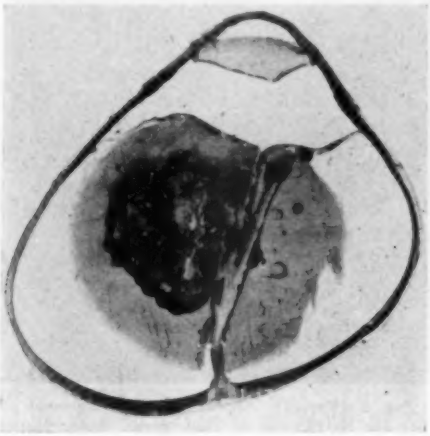

Fig. 2 (Perera). Low power photomicrograph of right eyeball containing retinoblastoma and complete separation of retina.

of a lesion situated so far anteriorly was likely to damage the eye and render it useless. Diathermic coagulation of such an accessible growth seemed to be the method of choice. If this should fail, radiation could always be employed later. The parents of the patient were informed of our reasoning, and agreed with the treatment planned.

Treatment. On November 22, 1948, under sodium-pentothal anesthesia, the sclera over the tumor was bared. The medial and superior rectus muscles were retracted by the use of silk sutures passed under their tendons.

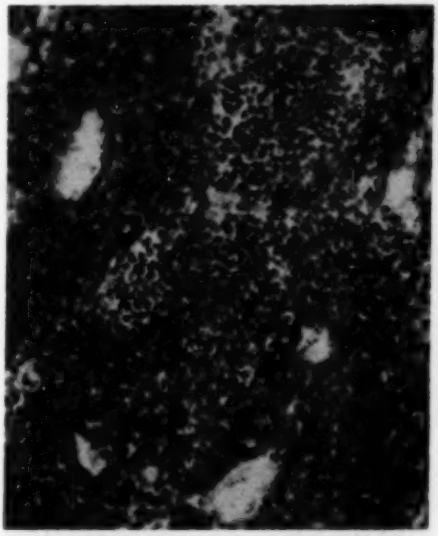

Fig. 3 (Perera). Photomicrograph of retinoblastoma under high power.

Two Pischel pins were placed posterior to the tumor, penetrating the sclera with diathermy using 40 milliamperes. Ophthalmoscopic observation showed that one pin was adjacent to the dilated retinal vein, which was coagulated at that point.

The growth was then outlined by a line of diathermic applications which extended well outside the retinal lesion and just behind the ora serrata in front of the tumor. The area within this space was then thoroughly treated, employing a 1.5-mm. penetrating electrode, each application lasting for three seconds. At the close of the operation, the treated area was completely coagulated. There was no vitreous hemorrhage.

Postoperatively, there was swelling of the involved site, followed by some shrinking and the development of pigmentation within the treated focus and by heaping up of pigment around its borders. There was a defect in the lower left field of vision corresponding to the coagulated area of retina.

The appearance of the tumor site on January 26, 1950, and on October 6, 1950, is shown in Figures 4 and 5.

Fig. 4 (Perera). Appearance of treated retina of left eye, showing replacement of tumor by scar tissue bordered by pigment (January 26, 1950).

The vision of the left eye was 20/25 on January 22, 1949, and has been 20/20+ since September 14, 1949. Measurement of the refraction of the left eye on September 27, 1950, showed a small amount of compound hyperopic astigmatism (+0.75D. sph. ⊂ +0.37D. cyl. ax 150°). Glasses were prescribed for reading, to relieve headaches. There has been no evidence of recurrence of the tumor up to the present time.

Summary

The literature dealing with the treatment of retinoblastoma by diathermic coagulation is reviewed. A case of probable bilateral retinoblastoma in a seven-year-old white boy is presented. The enucleated right eyeball contained retinoblastoma. The tumor of the left eye, situated in the upper nasal periphery, was treated by diathermic coagulation. There has been no recurrence for two years and three months following operation. The visual acuity of the treated eye is 20/20+.

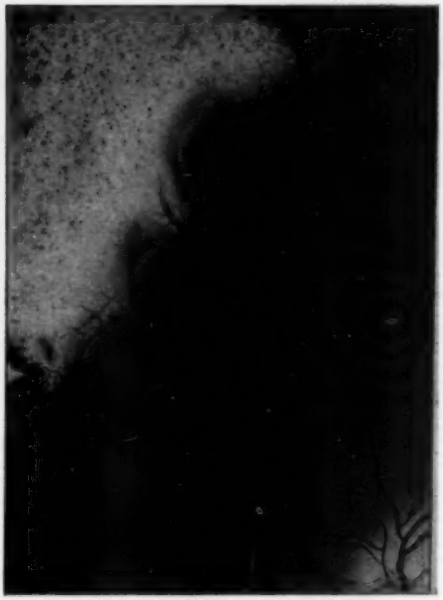

Fig. 5 (Perera). Appearance of background of left eye on October 6, 1950, drawn under higher magnification than Figure 4.

70 East 66th Street (21).

I wish to express my appreciation to Mr. Bethke for the drawings and to Mr. Lafayette for preparing the photomicrographs and the prints of the artist's drawings.

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MACULAR LESIONS OF VASCULAR ORIGIN*

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The origin of the macular lesions, discussed herein, from vascular disease is emphasized to set them apart from primary degenerative lesions on the one hand, and from inflammatory processes on the other.

The vascular damage productive of lesions of the macula lutea may affect the choroidal or the retinal circulation, or both simultaneously, and may be either organic or functional in character.

PART I

ORGANIC VASCULAR LESIONS LEADING TO DAMAGE OF THE MACULA LUTEA

A. ORGANIC LESIONS OF THE CHOROIDAL VESSELS

Secondary senile macular degeneration. Primary focal arteriosclerosis of the choroid has two sites of predilection—namely, the circumpapillary and the posterior polar regions. In the latter location, the consequences of atrophy of the choroidal stroma, and in particular the rarefaction and atrophy of the choriocapillaris, lead to severe damage of the pigment and neuro-epithelium of the macular retina and loss of central vision.

This secondary senile macular degeneration is a manifestation of advanced senility and usually affects both eyes, although often in very unequal degrees. It is relatively rare, and its severest degrees may show familial incidence (Sorsby,[1] Pillat[2]).

Clinically, the atrophic areas are yellowish white, well defined, with pigment flecks along the rim or scattered over them. Sclerotic choroidal vessels, some entirely transformed into white strands, others with a threadlike blood column, may remain discernible within these areas for a long time.

The histopathologic findings in this type of macular degeneration are illustrated in Figure 1, Case 1.

CASE 1

History. H. M., a woman, aged 80 years, complained of failing vision in the left eye for the first time six years prior to her death. She was first examined at the age of 72 years, when her vision was: R.E., 1.0; L.E., 0.8; and the fundi were normal. At the time of her first visual complaint, vision was: R.E., 0.8; L.E., to 0.1. There were faint pigmentary disturbances in the right macula, and in the left macula there was a more definitely circumscribed dense area of pigment proliferation. A diagnosis of bilateral macular degeneration was made.

During the following two years, macular pigment proliferation and rarefaction progressed slowly and the vision of the right eye diminished to 0.4.

After this period, symptoms of a circinate retinopathy developed in the right fundus in the form of small hemorrhages and scattered areas of white lipoid deposits above and below the macula. There were several hemorrhagic episodes in the right fundus during which a well-circumscribed round hemorrhage appeared in the foveal area.

Vision of the right eye failed much more rapidly during this time than the left and at the end of another four-year period it was reduced to 10/200 while the visual acuity of the left eye remained about 0.1.

During the last four years of her life, the systolic blood pressure varied from 190 to 230 mm. Hg, the diastolic from 80 to 160 mm. Hg, and she had frequent episodes of epistaxis.

Several months before her death from a cerebral hemorrhage, ophthalmoscopic examination revealed normal optic discs, marked retinal angiosclerosis, and scattered

* From the Department of Ophthalmology, Northwestern University Medical School. Presented before the Chicago Ophthalmological Society, March, 1951.

small superficial hemorrhages and lipoid deposits over both fundi.

In the left macula there was an area of choroidal and pigment atrophy, which measured about one and one-half disc diameters and which was surrounded by a zone of irregular pigmentation.

A grayish white lesion in the right macula was of the same size as the left, but was elevated about two diopters and of cystic appearance. Many fine blood vessels seemed to grow into it from the adjacent retina and from some signs of advanced senility such as atrophy of the sphincter iridis and a layer of hyalinized vessels of capillary size just behind it, fibrosis of the ciliary muscle, hyalinization of ciliary processes, and cystic degeneration of the retina at the ora serrata.

Posterior segment. The choroid as a whole appeared thinner than is usual in eyes fixed in Mueller's solution. There was marked thickening and hyalinization of the walls of the large choroidal arteries and narrowing of the lumen in some of them. The medium-

Fig. 1 (Klien) *Left eye of Case 1.* Senile macular degeneration secondary to choroidal sclerosis. Large defect of pigment and neuro-epithelium, extensive rarefaction of choriocapillaris, sclerosis of large choroidal arteries.

it was surrounded by a large ring of glistening white deposits.

The lesion in the left fundus retained its flat atrophic appearance to the end.

In the periphery of both eyegrounds, there were fine, dustlike pigmentary disturbances.

Histologic examination. Both eyeballs were removed about an hour after death and fixed in Mueller's solution.

The histologic examination revealed an uncomplicated secondary senile macular degeneration in the left eye, and a circinate retinopathy superimposed upon this degeneration in the right eye.

Left eye in Case 1: Secondary senile macular degeneration

The eye was sectioned in the horizontal plane.

The anterior segment was normal aside from some signs of advanced senility such as atrophy of the sphincter iridis and a layer of hyalinized vessels of capillary size just behind it, fibrosis of the ciliary muscle, hyalinization of ciliary processes, and cystic degeneration of the retina at the ora serrata.

Posterior segment. The choroid as a whole appeared thinner than is usual in eyes fixed in Mueller's solution. There was marked thickening and hyalinization of the walls of the large choroidal arteries and narrowing of the lumen in some of them. The medium-sized arteries appeared reduced in number and there was considerable rarefaction of the capillaries in a patchy distribution throughout the choroid. Some of the choroidal capillaries still present, especially those of the posterior polar region, were obliterated and showed hyalin degeneration.

Bruch's membrane was thickened and very prominent by the deep-blue stain of its elastic portion, which was most marked near the optic nerve. There was no defect of the membrane in this eye.

The pigment epithelium was missing in the macula over an area one and one-half disc diameters in size and, for a fourth of a disc diameter adjoining this defect, was of abnormal appearance, being represented by flat, unevenly pigmented cells of irregular size. Within this zone, the degenerating epithelial cells rested upon a thick layer of dis-

integrated granular material, which had the staining properties of the inner cuticular portion of Bruch's membrane and which gradually merged with this portion more peripherally, where the pigment epithelium became normal. There was a second zone of marked changes in the pigment epithelium in the equatorial region, where flat cells alternated with knoblike proliferations and drusen formation.

The large retinal arteries had somewhat thickened walls with many prominent vasa vasorum, but there was no narrowing of their lumina. In contrast, the small arterioles were hyalinized and had considerably reduced apertures. The capillaries of the superficial and deep vascular beds were seen with unusual clarity, especially in the macular region, and several had thickened walls and gaping lumina.

The macula. In the macular area there was a complete defect of the first retinal neuron, somewhat smaller than that of the pigment epithelium, suggesting the progression of the secondary degenerative process from the outside inward. The external and internal limiting membranes could be followed across the fovea centralis, but between them there was only a disorganized fibrillary structure containing a few nuclei. Between the external limiting membrane and the elastic portion of Bruch's membrane there were a few clumps of a granular cuticular substance, and a few isolated, misshapen pigment epithelial cells.

On the inner surface of the macular retina, fibroblasts, linked into chains of three or more cells, had started to form a thin membrane.

The optic nerve appeared normal.

Comment

The clinical differential diagnosis of senile macular degeneration secondary to choroidal sclerosis from the primary heredodegeneration, senile type, is not always easy and yet should be attempted, since therapeutic measures, for instance employment of anticoagulants,* may be developed in the future to influence favorably the degeneration secondary to the vascular process.

The findings most helpful in the clinical differentiation of these two conditions are the size of the macular lesion and some of the subjective symptoms.

Secondary senile macular lesions not infrequently reach considerable size, up to three and four disc diameters. These have been described also under the name of central areolar sclerosis (Nettleship). Within these large lesions an ample number of sclerotic choroidal vessels is usually exposed to view, which adds to the assurance of the correct diagnosis. But even in the early stages of this disease, choroidal vascular sclerosis becomes visible as soon as an area of pigment epithelium is destroyed, a detail which is lacking in the initial stages of the primary degeneration.

In the secondary degeneration there is a close correlation between the objective and subjective findings, while in the heredodegeneration the discrepancy between the severe visual disturbance and the inconspicuous ophthalmoscopic findings is often striking.

Histologically unless combined with an unrelated choroidal vascular sclerosis in very advanced old age, the primary degeneration, senile type, is distinguishable from the secondary degeneration by the well-preserved choriocapillaris and by the large defect in the first retinal neuron, which is more extensive than that of the pigment epithelium (Behr,[3] Klien[4]).

B. Organic lesions of the retinal vessels

1. Circinate retinopathy. Although not an etiologic entity, the clinical picture is typical and consists of the combination of two lesions—namely, the circinate lesion, which has given the condition its name, and a

* Investigations are under way to study the influence of anticoagulants on choroidal vascular disease and its retinal complications.

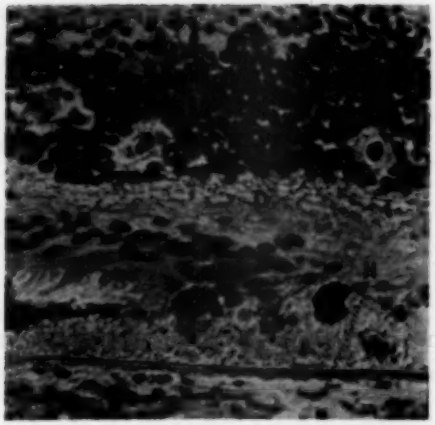

Fig. 2 (Klien) *Right eye of Case 1.* (D) Deep capillaries with hyalinized walls. (H) Hyalinized choroidal capillaries in perimacular region.

macular lesion, which may vary from an ill-defined, inconspicuous, grayish discoloration to a sharply outlined, often elevated area, resembling a disciform macular degeneration.

The circinate lesion is composed of sharply defined, brilliant-white, lipoid deposits, often intermingled with hemorrhages, which are arranged in a circle around the posterior polar region, usually inside the circle of the large temporal retinal vessels. It has been known to disappear completely, while the macular lesion tends to be permanent.

Circinate retinopathy is more often unilateral than bilateral, occurs almost exclusively in the aged, and affects women more often than men.

Eyes with this condition are only rarely obtained for histopathologic study. There are three reports in the literature, by Ammann,[5] Morax,[6] and Seefelder.[7] A fourth is added in the following:

Right eye of Case 1: Secondary senile macular degeneration with superimposed circinate retinopathy

The eye was sectioned in the vertical direction.

The defects of the pigment epithelium and of the first retinal neuron, the extensive destruction and rarefaction of the capillaries and of the medium-sized arteries of the choroid, and the sclerosis of the large arteries of the choroid and of the retinal arterial tree were similar to those of the left eye already described.

The size of the defect in the pigment epithelium and first retinal neuron was, however, smaller than that of the other eye. It has to be remembered that this was the better eye, with a less-advanced macular degeneration than that of the left eye, until the development of the circinate retinopathy.

Sclerosis of the precapillaries and capillaries of the macular region was, on the other hand, much more pronounced in this eye (figs. 2 and 3).

In great contrast to the flat expanse of the macular area in the left eye, the right macula was elevated by a mound of stratified, partly hyalinized connective tissue, which contained numerous slitlike spaces indicative of former cholesterol deposits (fig. 4). The main mass of this fibrous tissue was accumulated between Bruch's membrane and a thick band of cuticular substance, which obviously was a product of pathologic activity of the pigment epithelium.

This cuticular layer was by no means continuous, but had many breaks through which newly formed blood vessels had grown into the mound from the adjacent retina (fig. 5). No choroidal vessels were found to enter it as there were no defects in Bruch's membrane in the macular area.

The center of the foveal region was occupied by a cyst whose thin external wall was fused with the cuticular band. The cyst was surrounded by a dense irregular adhesion of this band to the remnants of Henle's fiber layer and of the outer nuclear layer. The zone of this adhesion contained clumpy remnants of the pigment epithelium and a large number of newly formed retinal capillaries.

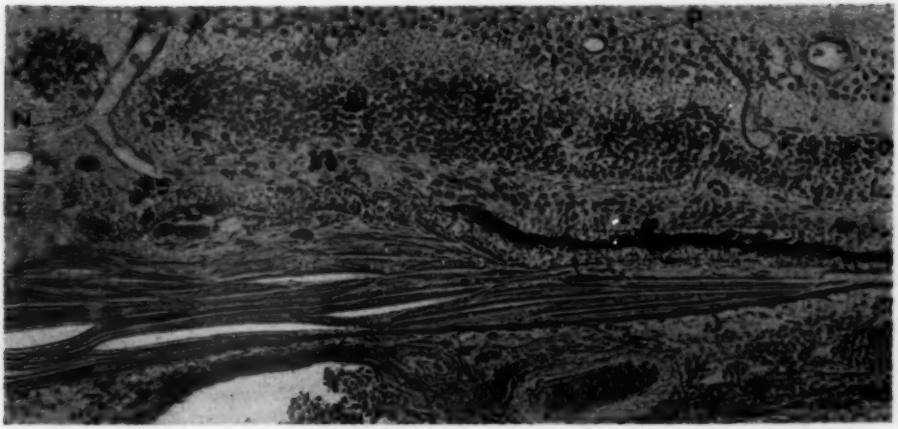

Fig. 3 (Klien) *Right of eye of Case 1.* (N) Sclerotic newly formed and (P) sclerotic preformed precapillaries and capillaries.

Peripheral to this adhesion there was a narrow, ring-shaped retinal detachment with an underlying deeply pink-staining coagulum.

Above and below the right macula, fatty granular cells in large and small groups infiltrated the middle and outer layers of the retina (fig. 6).

Near the inferior margin of the optic nerve, there were two breaks in Bruch's membrane, through which fibrous tissue and capillaries from the choroid had grown, separating the pigment epithelium from the membrane for a short distance.

Comment

In all specimens of circinate retinopathy studied histologically, the white deposits were made up of accumulation of fatty granular cells, often mixed with hemorrhagic detritus.

The macular lesions consisted of extensive cystic degeneration of the retina, the cavities being filled partly with serous tran-

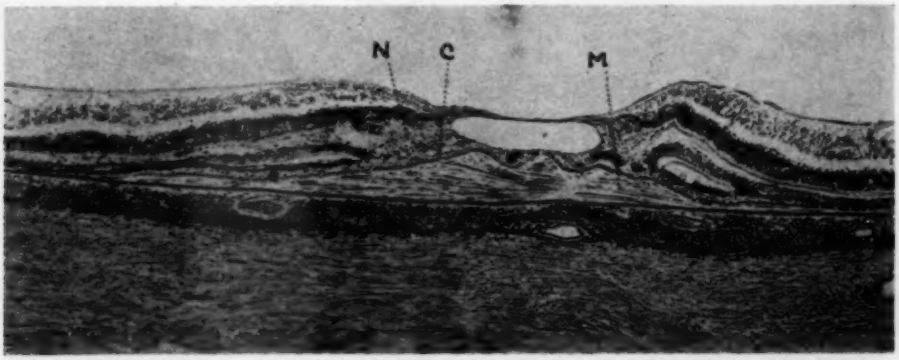

Fig. 4 (Klien) *Right eye of Case 1.* Circinate retinopathy superimposed upon macular degeneration. Fibrous mound (M) between well visible, intact Bruch's membrane and band of cuticular substance (C). (N) Newly formed capillaries.

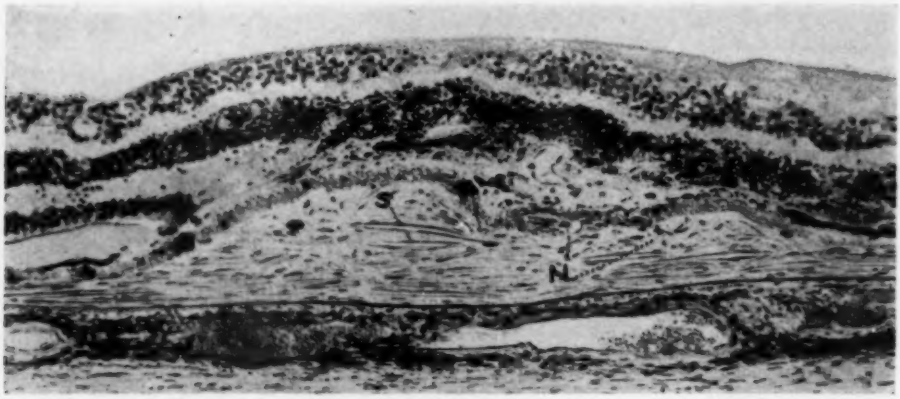

Fig. 5 (Klien) *Right eye of Case 1.* (N) New retinal capillaries growing into fibrous mound. (S) Cholesterol crystal slits.

sudate and partly with colloid masses (in the cases of Ammann and Morax, both of which represent a rather early stage of the disease). In Ammann's case there was marked sclerosis of the perimacular vessels and of the retinal arteries in general; in Morax's patient the sclerotic changes were limited to the perimacular small arterioles and capillaries, while the large retinal arteries were normal.

Seefelder describes, in addition to the extensive cystic degeneration of the macula, a narrow plate of fibrous tissue between choroid and retina in the macula. He found a very small break in Bruch's membrane behind it and a single thickened choroidal capillary herniating through it, and considers the choroid as the sole source of the fibrous tissue in his case, a pathogenesis identical with that of the disciform degeneration.

In Seefelder's patient, a macular degenera-

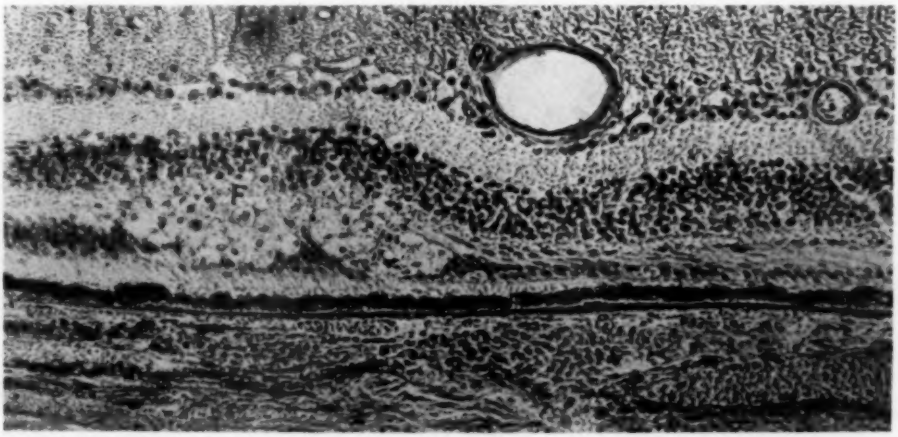

Fig. 6 (Klien) *Right eye of Case 1.* Nest of fatty granular cells (F) in retina, corresponding to white flecks of circinate lesion above macula.

tion was observed ophthalmoscopically in the other eye, which must have been of the primary type, as choroidal vascular sclerosis was completely absent and the choriocapillaris was well preserved in the fellow eye, which was examined histologically.

His case differed from the others by the absence also of retinal vascular changes, clinically and histologically, and he speculates at some length upon the nature of a retinal vascular disease which produced hemorrhages and serous extravasations without leaving histologically traceable organic alterations in the blood vessels.

In my case, the circinate retinopathy was superimposed upon a secondary senile macular degeneration but, since both eyes were obtained for histologic examination, the pathologic findings of the macular degeneration, which were almost identical in the two eyes, could be distinguished as separate from those of the unilateral circinate retinopathy.

Both Seefelder's and my cases represent an advanced stage of the disease with subretinal mounds of fibrous tissue in addition to the cystic degeneration of the macular retina.

In both the early and advanced cases of circinate retinopathy studied histologically, inflammatory processes in retina or choroid were absent.

Pathogenesis

Alterations of the precapillaries and capillaries in the perimacular area, of sclerotic nature in three of the cases reported so far but conceivably also of other origin, appear to be the basic pathologic process leading to circinate retinopathy.

The resulting anoxia of the perimacular tissue, and often decomposing hemorrhages, lead to the fatty deposits and seepage of edema into the macula, especially into Henle's fiber layer, thus causing cystic degeneration. Later seepage of hemorrhage from sclerotic perimacular precapillaries and capillaries and from some newly formed vessels, as was observed clinically on several occasions in the case reported here, may fill and rupture some of the cysts, permitting the hemorrhage to spread subretinally.

Events are thus set up which are similar to those occurring in disciform macular degeneration—namely, recurring hemorrhages, and their organization into a moundlike subretinal mass. The only difference between these morphologically so similar lesions is the source of the hemorrhage which derives, in the disciform degeneration, entirely from the choriocapillaris and not from the retina.

Verhoeff and Grossman[8] have stated that extravasation of blood or serum from the choriocapillaris may detach the pigment epithelium and reach the subretinal space through an apparently intact Bruch's membrane by diapedesis, although breaks of the membrane and herniation of choroidal capillaries through them are frequent findings in disciform degeneration. A mere absence of breaks in Bruch's membrane, therefore, would not exclude the choroidal origin of the macular hemorrhages in a case of circinate retinopathy.

In the case presented here, however, the disease was superimposed upon a secondary senile macular degeneration with extensive destruction of the choriocapillaris, and the hemorrhages were observed to occur repeatedly long after the senile macular degeneration was well advanced, facts which suggest a predominantly retinal origin of the hemorrhage.

This view is further supported by the new formation of retinal capillaries, also observed clinically, and by the marked sclerosis of the precapillaries in the perimacular area, revealed in the histologic preparation. The sharp outline of the small circular hemorrhage, which was observed twice in the foveal area of this eye during hemorrhagic episodes, suggests confinement of the hemorrhage within a cystic space and an intraretinal location.

However, some participation of the choroid also seems probable in this case, as suggested by the greater thickness in this eye

of the cuticular band produced by the pigment epithelium, which indicates greater irritation of its cells from the choroidal side than in the eye with the uncomplicated macular degeneration.

Accumulation of a serous transudate from the choroid underneath the pigment epithelium before its complete destruction could have initiated the production of this cuticular layer and could also have paved the way for rapid distribution in the same location of the later retinal hemorrhages.

Conclusion

Histopathologic examination of an eye with circinate retinopathy revealed pronounced sclerosis of the perimacular precapillaries and capillaries, which lends support to the conclusions reached by Ammann and Morax, that permanent alterations of the perimacular vessels, not necessarily of the same kind in all cases, lead to the early perimacular and macular manifestations of the disease.

The findings in the case presented here are especially conclusive, since the fellow eye, which was also obtained for histologic study and which did not show a circinate retinopathy, lacked an equal degree of sclerosis of the perimacular vessels.

The fibrous retroretinal mound which appears to characterize the advanced macular lesion of circinate retinopathy was considered to be of choroidal origin entirely in one of the two histologically studied eyes with an advanced lesion (Seefelder's), suggesting a coördinate vascular disturbance in the choroid. The rationale of such co-existing choroidal vascular processes has been discussed by Verhoeff and Grossman.[8] In the second eye, recorded herein, the correlated histologic and clinical findings pointed to a predominantly retinal origin of the extravasations, which resulted in the elevated macular lesion.

2. Central syphilitic retinopathy. A recurring central syphilitic retinitis, described first by v. Graefe[9] and later discussed in detail by Hirschberg[10] and E. Fuchs,[11] possesses the same characteristic subjective and objective symptomatology as the condition now commonly termed central angiospastic retinopathy.

The tendency for recurrence of this usually bilateral condition was considered by Fuchs to be due to syphilitic alterations of the perimacular retinal vessels. The resulting impairment of the circulation in this region was assumed to be of a minor degree, being compensated most of the time but representing, nevertheless, a predisposition for disturbances of the circulatory equilibrium from incidental and perhaps nonsyphilitic causes. In the light of our more recent conception of the pathogenesis of this recurrent macular disease, angiospasm alone could also account for the subjective and objective symptoms of the syphilitic disease.

The central syphilitic retinopathy herein discussed is of a different type, characterized by more conspicuous ophthalmoscopic findings and severe temporary visual disturbance, but not of a recurrent pattern.

Case 2

J. A., a Negro, aged 54 years, entered the eye clinic of Rush Medical College in 1935 with the complaint of poor vision of the right eye of three weeks' known duration.

Several months previously, an arterial hypertension with the systolic pressure varying from 185 to 210 mm. Hg, and a diastolic pressure from 110 to 115 mm. Hg, and an aortitis were discovered, and the blood Wassermann was found strongly positive. Antisyphilitic therapy was started at that time (bismuth and neosalvarsan).

Vision was: R.E., 10/200; L.E., 1.2.

There was considerable retinal angiosclerosis, mainly in the form of an obliterating endarteritis, and numerous, very fine, newly formed branches between the larger arteries. Many small flame-shaped hemorrhages were scattered over both fundi.

In the right macular area there were several groups of lipoid deposits and there ap-

peared to be a macular hole through which lipoid masses protruded (fig. 7). The optic disc was normal.

Vision of the right eye gradually improved and three years afterward it had returned to 1.2. The lipoid masses had disappeared and the macula had a normal appearance without any pigmentary disturbances. The original diagnosis of macular hole had to be changed to inner cyst rupture.

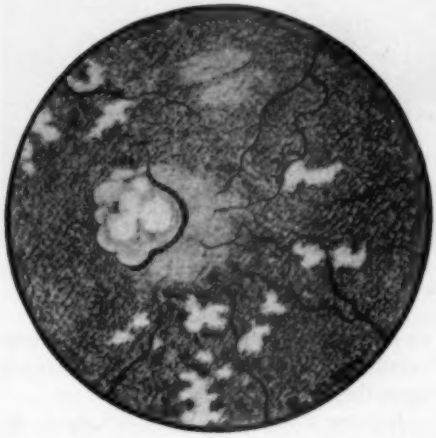

Fig. 7 (Klien) *Right eye of Case 2.* Central syphilitic retinopathy. Inner rupture of macular cyst, protrusion of lipoid masses. Vision 10/200; after three years, vision 1.2.

CASE 3

B. D., a Negress, aged 41 years, entered the eye clinic of Northwestern University Medical School in 1949, with the complaint of impairment of vision of the left eye of one week's duration.

For the past 10 years, she had received antisyphilitic therapy (bismuth and tryparsamide) and for the past five years she suffered from hypertensive cardiovascular disease with the systolic pressure varying from 156 to 220 mm. Hg, and a diastolic pressure from 100 to 110 mm. Hg.

At the time of the first ocular examination, corrected vision was: R.E., 0.8; L.E., 1/200.

In the left macula there was a reddish, well-defined area, one disc diameter in size, which was interpreted as a cyst. In its immediate neighborhood, there were a few small lipoid deposits. The optic disc was normal.

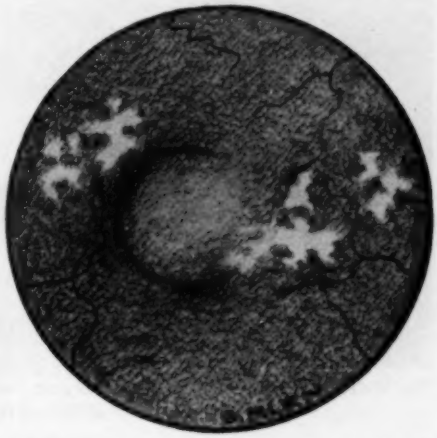

Fig. 8 (Klien) *Left eye of Case 3.* Central syphilitic retinopathy. Cyst filled with lipoid masses in foveal region. Vision 1/200; after one year, vision 0.8.

There was a considerable degree of retinal angiosclerosis in both eyes.

During the following two months the macular lesion became more prominent and yellowish white in color, appearing as a cyst filled with lipoid masses (fig. 8). The number of lipoid deposits in the adjacent retina had also increased.

In view of the great similarity of this macular lesion to the one described under Case 2, the prognosis regarding vision was considered to be favorable. This assumption proved to be correct.

Three months afterward, vision of the left eye had improved to 0.6. The macular area was flat again with a small reddish area below the fovea centralis. The scattered lipoid deposits were reduced in number.

At the present time, two years later, the left corrected vision is 0.8.

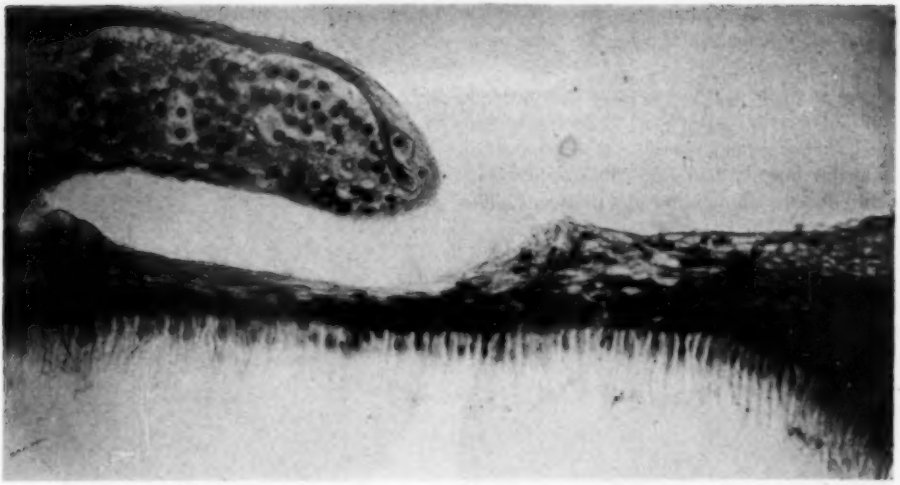

Fig. 9. (Klien). *Inner rupture of macular cyst.* Note well-preserved neuro-epithelium. Shrinking fibrous membrane on inner surface of retina was obvious cause for rupture.

Comment

The sequence of events in these two similar cases of central retinopathy, occurring in patients with syphilitic disease, appears to begin with a circulatory disturbance in the perimacular region, followed by stagnation of edematous fluid in the macula and later by cystic degeneration of the macular retina and deposition of varying amounts of lipoid masses, a series of events not unlike those occurring in circinate retinopathy.

The pathologic processes in the perimacular vessels, which cause the initial circulatory disturbance, seem, however, to regress under specific therapy and most of the retinal changes prove to be reversible. It stands to reason that systemic diseases other than syphilis, whose lesions have an affinity for the vascular system, could produce a similar picture, provided they damage the same portion of the retinal vascular tree.

The development of a retinal cyst, even in the macular area, does not necessarily mean an extensive destruction of retinal tissue. Macular cysts, filled with serous fluid or fatty detritus as in the two cases described above, may flatten again and become invisible clinically, leaving behind little or no visual disturbance. They also may rupture and the visual end-result depends upon the direction of the rupture.

Rupture toward the subretinal space destroys portions of the neuro-epithelium and a permanent central scotoma results. Occasionally rupture of the inner wall of the cyst toward the vitreous occurs, in which instance the neuro-epithelium remains intact and good visual acuity is recovered (fig. 9). Combined outer and inner cyst ruptures result in a macular hole and permanent loss of central vision.

Conclusions

Cases of central retinopathy which occur in the course of a systemic disease, as the syphilitic type recorded here, may form the link between the circinate retinopathy on the one hand and the central angiospastic retinopathy on the other, representing a prolonged but temporary damage to the same portion of the retinal vascular tree, whose progressive organic lesions lead to the permanent macular damage of the circinate retinopathy and whose transient, functional disturbances to the fleeting serous retinopathy of the angiospastic condition.

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OCULAR SYMPTOMS OF STELLATE GANGLION BLOCK*

Its use in the treatment of occlusion of the central retinal artery

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Introduction

In 1727, Pourfour-du-Petit noted softening of the eye following section of the cervical sympathetic. In 1815, Dupry noted injection of the conjunctival vessels and increase in the temperature of the ear after removal of the superior cervical sympathetic ganglion in a horse. In 1851, Bernard noted increased vascularity and elevation of surface temperature of the face after section of the cervical sympathetic cord in rabbits. In 1869, Horner described the symptoms resulting from a lesion of the sympathetic nerve supplying the head. These symptoms consisted of partial ptosis, miosis, and increase in skin temperature of the face on the homolateral side.

In 1889, the first sympathectomy on a human being was performed by Alexander in Liverpool. This was done in an attempt to relieve epilepsy. In 1896, the operation was repeated in a case of epilepsy and on a patient suffering from exophthalmos.

In 1899, Dr. James Ball excised the cervical portion of the sympathetic nervous system in a case of optic-nerve atrophy. About the same time the operation was used in an effort to relieve exophthalmos in cases of exophthalmic goiter.

Jonnesco and others employed the procedure in glaucoma. Dr. William H. Wilder, in 1903, stated that the operation was rather commonly used at that time to reduce intraocular pressure. In reading various case reports of that day, one is not impressed as to its effectiveness.

In 1916, Jonnesco resected the cervical sympathetic trunk for angina pectoris. About seven years later sympathectomy for Reynaud's disease and Hirschsprung's disease was used. The more modern methods of performing sympathetic denervation began about 1925 with Adson's and Brown's report on lumbar ganglionectomy for Reynaud's disease. At approximately this same time, Mandl discovered the importance of the thoracic cardiac nerves in the transmission of cardiac pain.

In the early 1930s diagnostic methods for temporarily interrupting sympathetic impulses with procaine made their appearance.

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* Presented before the Wilmer Residents Association, Baltimore, April, 1950.

About this same time, Royle reported the effects of sympathetic ganglionectomy in 14 patients suffering from retinitis pigmentosa. Other observers recorded observations during the next several years. Failure to gain permanent benefit in this disease is well known.

The lacrimal glands, salivary glands, and iris receive parasympathetic and sympathetic nerves. More recently parasympathetic and sympathetic innervation of the meningeal and cerebral arteries has been demonstrated. Uveal and retinal vessels are now known to be under sympathetic control, and possibly parasympathetic as well. There is good reason to believe the ciliary body and muscle receive sympathetic, as well as parasympathetic fibers (Cogan).

The parasympathetic supply to the head is by way of the third, seventh, and ninth cranial nerves. The fibers to the globe originate near the nucleus of the third nerve. The preganglionic fibers run in the trunk of the third nerve to the ciliary ganglion. As medullated, postganglionic fibers, they enter the globe as the short ciliaries.

So far as I am aware, no parasympathetic fibers have been shown to have an anatomic connection to the vessels within the globe. All of the sympathetic nerves to the head pass through the stellate ganglion, having been given off of the cord at the level of the eighth cervical and first and second thoracic as preganglionic fibers.

Walsh states that the fibers for the iris arise from the eighth cervical to the second thoracic; those to the ear and face from the third and fourth thoracic; and pilomotor fibers to the face and scalp from the fifth and sixth thoracic.

From the stellate ganglion, some sympathetic fibers emerge to join the vertebral artery and others continue to the superior cervical ganglion to form synapses there. Those accompanying the vertebral supply some of the cerebral vessels and also reach the eye possibly by way of the ciliary ganglion.

The postganglionic, nonmedullated fibers leave the superior cervical ganglion to continue along two routes: one by way of the internal carotid to the carotid and cavernous sinus plexuses, and the other along the distribution of the external carotid.

From the cavernous plexus the following branches are given off (Duke-Elder): (1) To the third nerve, (2) to the fourth nerve, (3) to the gasserian ganglion and to the ophthalmic division of the fifth (These are pupillodilator fibers and travel along the nasociliary to enter the globe with the long ciliary nerves and arteries.), (4) to the ciliary ganglion and then to the eye in the short ciliary nerves (This is probably vasomotor in function.), (5) to the ophthalmic artery and its branches.

From the carotid plexus the following arise: (1) A branch to the sixth as it crosses the internal carotid in the cavernous sinus, (2) branches which follow the ophthalmic artery and its various divisions including the central retinal artery, (3) connections by way of the deep petrosal and vidian nerves to the sphenopalatine ganglion and thence through the inferior orbital fissure to supply the periorbita, the muscle of Müller, and probably the lacrimal gland.

Stellate ganglion block

Interruption of the stellate ganglion produces the following immediate changes on the homolateral side—miosis, partial ptosis, dilatation of the conjunctival and retinal vessels, flushing of the skin due to dilatation of the capillaries, anhidrosis, and increased skin temperature. Also, in long-standing cases, the intraocular pressure is lower on the homolateral side by three to five mm.

In congenital sympathetic block, depigmentation of the iris is very common (Calhoun), but does not occur as a rule in acquired cases. True enophthalmos does not occur (Wagener).

Vascular effect

I shall confine the remainder of this dis-

cussion to the vascular effect of cervical sympathetic block. In 1939, Villaret and Cachera reported a remarkable experiment on a dog. These investigators noted marked vascular spasm in the pial vessels of the dog, making their observations through a window of the skull, after injection of pulverized glass or marble in the carotid artery. The spasm of the vessels was as widespread away from the areas of embolism as at the site. They observed the dilatation of the spastic vessels following interruption of the cervical sympathetics. Dilatation of the pial vessels, as observed through a skull opening, has also been seen in human beings following cervical sympathectomy (Volpitto and Risteen).

In 1931, Wagener reported his findings in a study of 35 patients on whom bilateral resection of the inferior cervical and first and second thoracic sympathetic ganglions was done.

Of the 35 patients, dilatation of the retinal arteries occurred in 34, bilaterally in 18 and unilaterally in 16. Dilatation of the veins was found in 25; being present in both eyes in 12 and in one eye in 13. Dilatation of both arteries and veins occurred in 34 eyes or 48 percent of the eyes examined. The arteries in some cases obtained a diameter of 75 to 100 μ and the veins a diameter of 100 to 125 μ. The highest percentage of dilatation of both arteries and veins was 25.

The minute-volume flow through a capillary tube of given length varies directly with the fourth power of the diameter of the tube. For example, a 22-percent increase in diameter would allow 150-percent increase in blood flow. In the cases in which dilatation occurred, the average dilatation of the arteries was 13 percent and of the veins, 15 percent.

The operation was performed in these cases for Reynaud's or Buerger's disease or for scleroderma. There were two cases with arthritis. Wagener found that enophthalmos did not occur as a result of sympathetic block.

In summary, Wagener states that dilatation of the retinal arteries occurred as frequently as narrowing of the pupils and fissures and dilatation of the retinal veins somewhat less frequently. In most cases dilatation of the vessels seemed to be more transient than the narrowing of the pupils and fissures, although it seemed to persist for as long as a year in some cases.

For perhaps 10 or 12 years stellate ganglion block has been used extensively for the relief of arterial spasm and to increase circulation in the upper extremities, particularly in Buerger's and Reynaud's diseases and in cases of trauma.

In the past few years, stellate ganglion block with novocaine has been used more and more as an emergency treatment of apoplexy, especially in those cases thought not to be due to hemorrhage. It is almost a routine procedure in some clinics and, in cases of cerebral accident due to embolus or arterial-spasm, and in many cases of thrombosis, the results reported are very startling.

All of the authors emphasize the fact that the cases must be treated early, preferably within the first six hours after the onset of the atttack. Aphasias, hemiplegias, and mental confusion have been observed to improve within 15 to 20 minutes following the stellate ganglion injection. The injection is often repeated daily for some days or even twice daily.

One author devised a method of continuous stellate ganglion block with novocaine by means of a vinylite plastic tubing which was threaded through the needle and allowed to remain in place.

A recent case of Dr. Harry Wilkins, Oklahoma City, is of interest. Dr. Wilkins ligated the right internal carotid artery because of an inoperable cerebral aneurysm. Eighteen hours later contralateral hemiplegia and left homonymous hemaniopia developed. Novocaine injections of the stellate ganglion produced enough vascular dilatation, by relief of spasm, to restore completely the visual fields and leave only a very

slight left-sided weakness. The man drives a truck daily now.

A more recent example was a patient on the neurosurgical service of the Oklahoma University Hospital. He had a hemiplegia and mental confusion of a few hours' duration. Stellate block resulted in immediate and dramatic improvement. Fifteen minutes following the block he seemed clear mentally and began to move the affected arm and leg. He recovered with no residual effects. The literature is showing more and more reports of similar cases.

Case report

My personal interest in this problem was stimulated by a case of embolus of the central retinal artery which came under my care several months ago. The patient was a young man, aged 26 years, who stated that he had suddenly lost all light perception in his remaining eye four hours before I saw him. He had lost his other eye in childhood as a result of some injury. He stated that he had no light perception for about three hours and then the vision in the eye had improved to some extent.

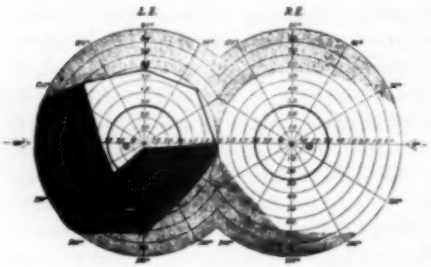

Fig. 1 (Coston). Visual field (January 13, 1950) before stellate ganglion block. Test object, one-degree white. Vision, 20/15.

At the time of my original examination he had normal central visual acuity through a very narrow field (fig. 1). A study of the fundus revealed a transparent embolus lodged at the first bifurcation of the superior temporal retinal artery. The arteries of the entire fundus seemed narrow and there was tremendous spasm of the remainder of the branches of the temporal artery beyond the point of the embolus. The retina was becoming grayish and edematous over the area supplied by the superior temporal artery, including the macula.

One gr. of papaverine was administered intravenously without producing any change in the retinal condition. Inhalation of five or six ampules of amylnitrite in rapid succession was of no avail.

The patient was sent immediately to the hospital and the neurosurgical resident did a stellate ganglion block with novocaine approximately five and one-half hours after onset of the visual loss. Fifteen minutes after the injection, the resident noted a marked dilatation of the entire retinal tree and saw the embolus pass out into the periphery of the fundus. The patient exclaimed immediately that the vision had improved.

I observed the fundus about an hour after the ganglion block and noted marked dilatation of the retinal arteries and veins throughout the entire fundus. The embolus had lodged in the extreme periphery at one of the finer bifurcations of the superior temporal artery. During the next several days, the retinal vessels gradually became smaller and the embolus disappeared from view. He has shown no recurrence of symptoms (fig. 2).

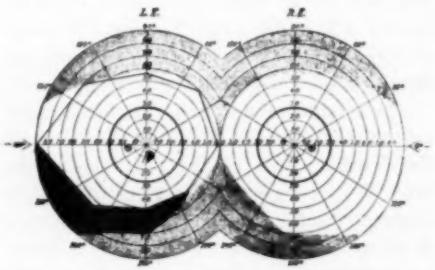

Fig. 2 (Coston). Visual field (January 27, 1950) two weeks after stellate ganglion block. Test object, one-degree white. Vision, 20/13.

Present studies

At the present time, studies are being made on the effect on the retinal vessels of stellate novocaine block in cases of hypertension and in toxemias of pregnancy. I am using an apparatus devised by Dr. Wilbur Rucker for measuring the size of vessels ophthalmoscopically. Its accuracy far surpasses any previous method known to me.

It is hoped that evidence for or against sympathectomy in cases of hypertension may be forthcoming. One should be able to differentiate vasospasm from fixed vessel changes in the retina.

One such case of toxemia of pregnancy, which I observed, illustrated this very nicely. Novocaine block of the stellate ganglion brought about a marked dilatation in the retinal arteries on the homolateral side. The dilatation was uneven, even in the same vessel, being reduced or nil in sections of the vessel showing obvious fixed changes in the walls.

This same patient showed the same type of dilatation of the retinal arteries following 400 mg. of novocaine given intravenously. The degree of widening was less marked. The dilatation following novocaine intravenously was bilateral but was on the homolateral side only at the time of the stellate block. A retrobulbar injection of novocaine failed to produce any change in the retinal vessels of this patient.

I believe the explanation for this is the fact that the sympathetic fibers for the retinal vessels accompany the central retinal artery and are protected by the optic-nerve sheath from the novocaine. I do not believe that even a deep orbital injection of novocaine would reach these fibers ordinarily. At least in my hands it has failed to do so.

Discussion

All of us have seen quiet, sudden homonymous field defects develop without other symptoms or signs. Many of these patients give a history of having experienced transient visual failure in the past. These are undoubtedly cases of cerebral spasm or thrombosis or embolus. Novocaine stellate block should be done early in all cases exhibiting sudden visual failure thought due to vascular occlusion either in the eye or cerebral in origin.

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PHOTOPHOBIA: MECHANISM AND IMPLICATIONS*

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The attempts so far made to explain the mechanism of photophobia fail to account adequately for all the phenomena observed. Photophobia is a common but important symptom and a knowledge of the underlying factors is prerequisite for rational management. Photophobia is usually a pathologic condition and the term is applied correctly when light induces or exacerbates pain in the eye.

Dazzling, though confused with photophobia, is simply a discomforting sense of excessive brightness. The cause of dazzling is generally inadequate adaptation, which may be either temporary and occur physiologically; or permanent as in albinism, total color blindness, and central scotomas. It can also result from diffusion of light through the ocular media by the veiling glare incident to opacities in the cornea, lens, or vitreous.

Dazzling, in contrast to true photophobia, is not accompanied by blepharospasm and lacrimation. The closed lids exclude about 99 percent of the total light flux and the spectral distribution is modified by their blood content. The lids are thus highly efficient in protection from dazzling but, with pathologically sensitive eyes, photophobia may still continue.

That the integrity of the fifth nerve is essential to photophobia was proved by Krause in 1896 when he discovered that his operation of removing the gasserian ganglion for the relief of trigeminal neuralgia abolished this reaction from the eye on the operated side but not from the eye on the normal side.

In 1901, Nagel[1] tested the suggestion of von Frey that photophobia was probably dependent on the pupillary light reaction and found, on dilating his own pupils with homatropine, that no photophobia occurred on passing suddenly from darkness to sunlight, though the dazzling was greater because of the increased light entering the eyes.

This observation was confirmed by Fuchs[2] and supported by Axenfeld,[3] who stressed the usual amelioration of photophobia by mydriatics, but Römer contended that the reaction of the iris could not be the basis of photophobia since physostigmine did not reproduce the photophobic syndrome in sensitive eyes. In its effect on pupillary contraction, however, light acts very much faster than physostigmine. The maximal response from light is attained in 0.8 second; whereas, that from physostigmine occurs in five to 15 minutes. The speed of reaction probably accounts also for the greater photophobia experienced when the sensitive eye is tested with the same light as the normal eye since the pupil reacting consensually takes longer to attain its final constrictive size.[16]

Feilchenfeld[4] showed that photophobia cannot be due to increased retinal sensitivity since dark adaptation greatly increases light sensitivity and only slightly affects photophobia. That the retina itself is insensitive to pain was established by Magendi.

The fallacy of the suggestion that the nerves of common sensation may be directly stimulated by light energy was beautifully demonstrated by Siegwart[5] who found that only rays from the visible spectrum produce photophobia. He showed also that the reaction to spectral colors was determined by their respective luminosity and the consequent effect on pupillary constriction. Moreover, no absolutely blind eye evinced the slightest photophobia on direct exposure to light, if the healthy eye was shielded; but if the consensual pupillary reflex was pre-

* From the Department of Ophthalmology, Northwestern University Medical School. Read by invitation before the St. Louis Ophthalmic Society, March 2, 1951.

served, the blind eye reacted with pain when the seeing eye was illuminated.

Photophobia is manifest most frequently in diseases of the anterior part of the eye but may accompany a lesion in any area supplied by the ophthalmic division of the fifth nerve such as head injury, subarachnoid hemorrhage, infective or reactive meningitis, acromegaly, trigeminal neuralgia, or migraine.

Peters[6] emphasized that trigeminal hyperirritability must be an essential factor in the pain caused by the pupillary reaction, as his patients with chronic photophobia often complained of asthenopia, independent of refractive error or muscular imbalance, and generally their supraorbital nerves were abnormally sensitive to pressure.

Light is particularly distressing in disturbances of the cornea, and the more superficial the corneal lesion is, the more severe the photophobia—evidently because of the epithelial distribution of the corneal nerve endings.

If the pupillary reaction to light is the key to photophobia, what mechanism explains the wide variety of exciting lesions? What accounts for the greater photophobia in corneal disease than in iritis and why is the abatement of photophobia by mydriatics not uniformly complete?

The trigeminal axon reflexes producing vasodilatation and hyperalgesia provide a rational answer. Irritation of the fifth nerve, as by a foreign body on the cornea, causes a pupillary constriction—the trigeminal pupillary reflex—which is probably due solely to a reflex vasocongestion of the iris.

Bruce, in 1913, showed that this reflex of vasodilatation was dependent on the integrity of the trigeminal nerve and did not occur after removal of the gasserian ganglion and subsequent complete degeneration. It has been established since that all nerves of common sensation contain vasodilator fibers whose cells of origin are in their sensory ganglions. The phenomenon has been termed antidromic vasodilatation; and the mechanism, the axon reflex. In a patient operated for trigeminal neuralgia a bit of mustard plaster placed above the brow of the affected area will elicit the reaction of vasodilatation after retrogasserian neurectomy—but not if the ganglion was removed.

In 1934, I suggested that the vasodilatation of the trigeminal pupillary reflex was the sensitizing factor that made the pupillary light reaction painful.[7] In support of this view, I found that instillation or subconjunctival injection of epinephrine (1:1,000) relieved photophobia in chronic conjunctivitis, corneal disease, and iritis.

In normal anesthetized eyes the miosis of vasodilatation that followed instillation of 10-percent histamine induced photophobia, but no photophobia occurred with the miosis of physostigmine. In a patient whose right superior cervical ganglion had been removed previously, the postoperative photophobia in the right eye was controlled readily by the use of epinephrine.

Vasodilatation consequently appeared to be as essential to the exhibition of photophobia as the presence of the three other factors—vision, oculomotor function, and sensation.

Vasodilatation is mediated through the release of histamine. The ciliary spasm often present in ocular inflammation is probably a histamine-induced contracture and hence is not counteracted by atropine. After severe contusions of the eyeball, temporary myopias of four and six diopters have been observed to persist under atropinization.

In the atropinized, inflamed eye Vogt saw with the slitlamp a definite iridic contraction. My tests indicate that in the irritable eye, the ciliary body as well as the iris may respond to light.

To one side of the eye being refracted a 200-watt bulb was placed at an angle of 30 degrees. The refraction was then determined when this light was turned off and on. With normal eyes the light made no difference; but in persons with corneal lesions and photophobia whose vision could still be brought to normal with lenses, the turning

on of the side light necessitated an additional minus 0.25D. sph. to minus 0.75D. sph. to attain the same acuity.

Thomas Lewis[8] maintains that hyperalgesia like vasodilatation is mediated by axon reflexes, but hyperalgesia does not usually appear until clear signs of inflammation are established. The interplay of light, oculomotor function, trigeminal sensation, and trigeminal vasodilatation and hyperalgesia are necessary to evoke the pain of photophobia. The increased blinking reflex is a secondary result, and not a causative factor in photophobia, for surgical observation demonstrates that photophobia continues after akinesia of the orbicularis muscle and is not abolished until after the retrobulbar injection takes effect.

Magitot[9] agreed with my theory in part but objected that it did not explain the relief of photophobia produced by anesthetizing the region of the sphenopalatine ganglion, a procedure which he still practices.[10]

However, Kime[11] makes the unequivocal statement: "There are no sensory ganglion cells in the spheno-palatine ganglion; hence, no sensory synapse occurs within the ganglion and it cannot mediate referred pain or act as a sensory switchboard."

Proetz[11] feels that the apparent effects of anesthetizing this ganglion must be produced indirectly through vasomotor changes.

The most recent investigation of photophobia has been made by Eckhardt, McLean, and Goodell.[12] Their study was inspired by H. G. Wolff and is incorporated with modifications in his recent monograph on head pains.[13] In this research no distinction is made between dazzling and photophobia, though the original paper admits that in normal individuals excessively bright light never produced true pain.

The blinking rate was selected as a valid criterion of the degree of photophobia—a choice that is hard to justify since Wolff[14] himself says: "For marking the threshold of pain the verbal report of an instructed subject is the most reliable evidence. Pain is a perceptual experience of sensation, and not a muscular, or glandular, or other reaction. . . . The age-old linkage between perception of pain and reaction to its has filled the vast literature . . . with irrelevancies and contradictions."

If photophobia has a photomotor basis, no true photophobia can occur in patients with the Argyll-Robertson syndrome as their pupils do not respond to light. Strangely enough in such patients no increase in the blinking rate is produced by dazzling also, even with maximum mydriasis.[12] This adds to the evidence that the optical blinking reflex is subcortical and mediated via pupillomotor fibers. This paper, which has been popularized in recent texts,[15,16] maintains that the sensation of a photophobia is located for the most part in the central neural connections and suggests as a logical explanation that in hyperalgesia involving the trigeminal area, pain and light intensify each other.

Present investigation

Recently I re-investigated the subject by determining the threshold stimulus of light required to produce photophobia, using for this purpose spectacles with rotating polaroid filters to which protractors had been affixed. Two types of different density were used (table 1).

TABLE 1

VISUAL TRANSMISSION OF SUPERIMPOSED POLAROID FILTERS

Setting Angle (Degrees)	Visual Transmission in Percent	
	Type A	Type B
0	9.1	23.0
10	8.9	22.2
20	7.9	20.3
30	6.3	17.0
40	5.0	13.3
50	3.5	9.9
60	2.2	6.0
70	1.1	2.6
80	0.3	0.7
90	0.01	0.01

Type A refers to the Beck-Lee variable density filter made for the U. S. Navy in

World War II. In this type the filters are of neutral color and rotate synchronously before both eyes. In Type B—the polaroid variable light sunglasses, Model 150—the filters have an added bluish tint and rotate independently. The visual transmission of the crossed polaroids (setting 90) in each type was less than 0.01 percent, which under all circumstances prevented photophobia.*

The degree of photophobia was measured by the percentage of light transmitted through the polaroids at the first excitation of pain. If the transmission of rotating polarizers is known when placed parallel (setting zero), the transmission at any certain angle A can be found by multiplying this value by the square of the cosine of angle A. The increase in intensity on rotation from 90 to 0 follows a typical curve (fig. 1), similar to the sine^2 curve illustrating Euler's familiar theorem on the vertical components of cylinders at oblique axes.

The tests were made in a darkened room with the patient wearing the rotating polaroid spectacles placed at setting 90 and a slip-on occluder before the normal eye. A light of 100 foot-candles at one foot distance from the photophobic eye was turned on, and the polarizer gradually rotated until the patient first perceived definite ocular pain. If no photophobia resulted with the trial of the denser polaroid, the test was repeated with the less dense filter.

After a reading was determined the test was repeated more rapidly to check the reliability of the finding. The variations were seldom more than five degrees. The direct and consensual pupillary reflexes gave approximately similar results.

The affected eye was then treated with two instillations of epinephrine (either 1:1,000 or 1:100), two minutes apart and the measurement of photophobia was made 10 minutes later.

Other tests were made after one instillation of neosynephrine (10 percent); after mydriasis with homatropine (five percent) and atropine (one percent); and after inhalation of 15 drops trichlorethylene (chlorylen). The results in Table 2 show that epinephrine consistently reduced photophobia in cases due to conjunctival, corneal, and iridic disease, or due to head injury or migraine. The value of trichlorethylene in reducing trigeminal irritability is substantiated, as likewise is the efficacy of mydriatics in the control of photophobia.

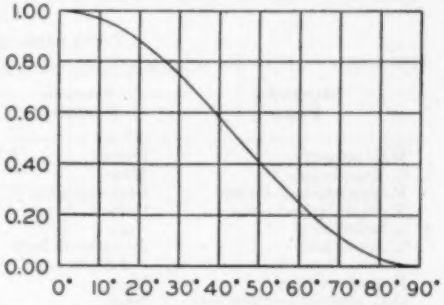

Fig. 1 (Lebensohn). Relative transmission of light through superposed polarizers.

Discussion

Wolff distinguishes independent mechanisms for photophobia placed at the level of the pupil, the brain stem, and the cortex respectively. The pupillary contraction to light is recognized as the cause of photophobia in iritis only. In all other cases, he interprets photophobia as the interaction of the sensations of light and pain either in the brain stem or in the cortex. "The entire central mechanism of the sensory trigeminal including the mesencephalic root and nucleus constitute together with the optic nerve the neural mechanism for photophobia."[13]

If this is true, why is the symptom of photophobia limited only to the territory of

* The Beck-Lee variable density filter is no longer regularly manufactured but is available as war surplus from the Capitaine Distributing Company, 435 90th Street, Brooklyn 9, New York, at the close-out price of three for $5.00; the Polaroid variable sunglasses, Model 150, distributed by the American Optical Company, retail at $12.50.

the ophthalmic branch of the trigeminal innervation? Wolff is of the opinion that photophobia is less frequently ocular than neurologic in origin: "Although photophobia is a dramatic accompaniment of eye disease, it is most often a manifestation of noxious impulses arising in head structures other than the eye."

These sweeping neurologic conceptions are wholly based on sundry observations of the increased blinking rate apparently associated with photophobia. The blinking reflex is influenced by dazzling, menace, tactile stimuli, and emotional tension. Nevertheless, it was selected as the criterion of photophobia as it seemed to be "the only accurately measurable component."

From this study came the odd verdict that, in the normal eye, photophobia is relieved by surface anesthesia and increased by cycloplegia—a naïve conclusion that contradicts the observations of Nagel,[1] Fuchs,[2] and Axenfeld.[3] Since epinephrine should not be expected to reduce the increased blinking rate produced by dionin or a foreign body, its failure to do so is no warrant for the dogmatic assertion that "vascular congestion is not a factor in photophobia."

In the progress of ocular symptoms, pain, discomfort, or foreign body sensation come first, then blepharospasm and tearing, and finally photophobia. A minute corneal ulcer due to herpes or an ingrowing lash gives rise early to a foreign-body sensation or pain, tearing, and blepharospasm; but photophobia may be absent.

In a case of extensive erosion of the cornea due to pontocaine sensitivity, photophobia was extreme and, after atropine treatment for two days, the globe was still congested; pain, tearing, and blepharospasm though diminished were still present; but true photophobia was no longer measurable.

Photophobia takes time to evolve; hence it cannot be produced satisfactorily in normal eyes by inserting a small silk thread in the cul-de-sac or even by the procedure of injecting 0.3 cc. of six-percent sodium chloride into the frontalis muscle above the brow—as was practiced by the neurologists in their study.[12]

TABLE 2

TESTS MADE WITH VARIOUS DRUGS

Illustrative Cases	Previous Treatment	Light causing (Photophobia)	Present Treatment		Light causing (Photophobia)
R.E. normal	Dionin	11.5	Adrenalin	0.1%	21.5
L. head injury	None	5.3	Adrenalin	0.1%	11.5
R. vascularized cornea	Beta radiation	2.8	Adrenalin	1.0%	5.6
R. vascularized cornea	Cortone drops	5.6	Adrenalin	1.0%	11.5
L. acute iritis	None	0.6	Neosynephrine	10%	4.0
L. acute iritis	Atropine & fever 2 days	5.9	Adrenalin	1.0%	100.0
R. serpent ulcer	None	6.0	Adrenalin	0.1%	17.0
O.U. chronic conjunctival hyperemia	None	3.5	Adrenalin	0.1%	22.2
L. migraine	None	4.0	Adrenalin	0.1%	22.2
R. marginal corneal ulcer	None	6.3	Chlorylen inhal.		100.0
R. marginal corneal ulcer	None	1.9	Chlorylen inhal.		5.0

On trying the salt injection on myself, a severe ache developed in a few seconds in the brow radiating down the side of the nose to the tip and lasted less than five minutes. It was accompanied by tearing and blepharospasm but noticeable photophobia was evanescent. The pupil on the affected side became slightly smaller. The browache continued in subdued form for 30 minutes and was accompanied by a burning sensation in the eye, as if a too strong zinc solution had been instilled. No photophobia was measurable during this period but there was a vague

discomfort increased by reading, which disappeared after the instillation of epinephrine (1:1,000).

Implications

In serious ocular disease, the increase or decrease of photophobia is significant as a guide to the progress of the causative lesion. Peters[6] rightly emphasized the association of photophobia and asthenopia in chronic conjunctival hyperemia. According to my view, both symptoms stem from the pupillary contraction of a reflexly congested and irritable iris which can be produced by light or by the near reaction.

The clinical relief afforded by the instillation of epinephrine or sympathomimetic drugs (privine, neosynephrine) testifies to the significance of vasodilatation in the causation of this syndrome. If the entity of conjunctival asthenopia was more widely recognized, fewer patients would be wearing negligible corrections, tinted glasses, or lateral prisms.

In allergic conjunctivitis, as exemplified by vernal catarrh, itching and photophobia are commonly associated. Histamine is productive of itching and also mediates vasodilatation. Since epinephrine is the physiologic antagonist to histamine, its local use for symptomatic amelioration has a logical basis.

In sensitive eyes, a light transmission of two to six percent may be sufficient to cause photophobia (table 2). The variable density polaroid filters, especially the denser type, can effectively control this symptom.

To prevent dazzling, Farnsworth[17] asserts that sunglasses should have only 20-percent transmission for street wear, 10 percent for outdoor sports. Any sunglass that gives more than 30-percent transmission is of little value in preventing dazzling, much less photophobia. The commercial companies have been entirely too conservative in this direction (table 3). Only the darkest shades of the standard varieties should be ordered for prescription sunglasses.

Therapy

Anesthetic drugs are dangerous to the integrity of the cornea and should be prescribed seldom in spite of the ready relief they give to pain, blepharospasm, and photophobia. An exception may be the one-dose ampule of pontocaine ointment (an item of clinical investigation) which I have supplied to patients with actinic keratitis and after spud-removal of a foreign body. Every local anesthetic inhibits cell migration and mitosis and tends to loosen the adhesion of the corneal epithelium.

Pain and photophobia can be alleviated by internal medication if judiciously directed both to raising the threshold of pain and altering the patient's mood and reaction. Among the remedies in the first group are salicylates, antipyretics, methadon, and inhalations of trichlorethylene; in the second group belong the time honored Spiritus frumenti, caffeine, amphetamine, and the barbiturates. Hypnotics have a special value as corneal healing is favored when both eyes are closed in sound and prolonged sleep.

If the patient is not relieved adequately

TABLE 3

Percent visual transmission of tinted lenses

Cruxite	A–88	AX–83	B–72	C–52	D–23	
Soft-Lite	1–86	2–82	3–73	4–46		
Calabar			B–67	C–51	D–36	
Fieuzal	A–87		B–63	C–40		
Smoke	A–86		B–60		C–32	D–17
Ray-Ban			1–73	2–54	3–30	4–11
Welding*						4–9.5

* In welding glasses the transmission decreases further from shade 6 (1.5 percent) to shade 14.

by this regimen, a retrobulbar injection of alcohol is indicated. No undue reaction occurs if a small amount only is injected. After a retrobulbar injection of one cc. of two-percent procaine, the needle is left in place and 0.5 cc. of 63-percent alcohol is injected (two parts 95-percent alcohol to one part water). I recall a case of vernal catarrh in which the cornea was injured inadvertently by a flake of carbon dioxide snow. The instillation of a local anesthetic and the injection of morphine failed to control the resulting pain and photophobia. One retrobulbar injection of alcohol completely relieved the patient's suffering until healing took effect.

To relieve severe supraorbital pain in acute iridocyclitis, Richter[18] has injected into the region of the supraorbital nerve 0.5 cc. of 0.2-percent eucupin in one-percent procaine. The efficacy of the treatment suggests that this pain arises from the contracture of sustained blepharospasm.

Summary

Variations in the intensity of photophobia can be accurately evaluated by means of rotating polaroid filters. Such tests demonstrated that photophobia, regardless of etiology, is measurably alleviated by epinephrine, neosynephrine, mydriatics, and inhalations of trichlorethylene.

Photophobia may accompany a lesion in any area supplied by the ophthalmic division of the trigeminal nerve. Whatever the cause, true photophobia is based invariably on the iridic constriction to light which is the only reaction that light effects which is demonstrably capable of producing pain. The pupillary light reflex is not painful ordinarily and only becomes exquisitely so after the iris has been sensitized by the trigeminal axon reflexes producing vasodilatation and hyperalgesia. This common factor, the trigeminal pupillary reflex, is the link connecting all sources producing photophobia.

The blinking reflex is not a valid criterion of photophobia. Deductions based thereon and lacking other support are obviously without significance.

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INFLUENCE OF MICROWAVES ON CERTAIN ENZYME SYSTEMS IN THE LENS OF THE EYE*

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Microwaves have been shown to cause cataracts according to reports by Daily and co-workers[1, 2] and by Richardson and associates.[3] This is probably one of the simplest methods yet devised for the experimental production of cataracts.

Cataracts formed by exposure of the eyes of rabbits to microwaves are of two types. In one type the cataract is present immediately after exposure to microwaves, when the region of the lens under the capsule is diffusely involved. The cataract progresses rapidly until the entire lens becomes opaque. This type is seen only when grossly visible damage to other ocular structures is produced; namely, clouding of the cornea accompanied by congestion and hemorrhages into the iris and ciliary processes (fig. 1).

Fig. 1 (Daily, *et al.*). The posterior surface of the iris and ciliary region of the eyes of an albino rabbit immediately after exposure to microwaves. Note the hemorrhage and congestion in the exposed eye.

The second type of cataract which follows exposure of the eye of a rabbit to microwaves is not associated with obvious gross clinical signs of injury, although dissection and microscopic examination of some eyes

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containing such cataracts have demonstrated the presence of hemorrhagic infarcts in the ciliary processes.

This type of cataract does not appear immediately after exposure to microwaves, but becomes visible only after a time varying from several days to several weeks. It is limited to the posterior cortex, but may be made to progress and involve the entire lens by repeated exposure of the eye to microwaves. Figure 2 shows a circumscribed, posterior cortical cataract of this type.

Fig. 2 (Daily, *et al.*). Photograph of a circumscribed, posterior cortical cataract produced by exposure of the eye of a rabbit to microwaves.

Exposure of the eye of a rabbit at a distance of two inches from Director C (the corner reflector) with an output of 94 watts from the microwave generator, for a duration of 10 minutes, may produce either of the above-mentioned types of cataracts.

Under these conditions, the temperature of the vitreous directly behind the lens was determined by the use of the thermistor in 12 rabbits 15 seconds after the microwaves were turned off.

The temperature ranged between 47°C. and 54°C. This variation in the rise of temperatures of the ocular structures during exposure may be the cause of the variability in the degree of damage to ocular structures of different animals after exposure to microwaves under identical experimental conditions.

In addition to a follow-up of the development of cataract in the eyes of rabbits exposed to microwaves, the activity of certain enzymes in the lenses of the eyes of rabbits and other animals was investigated. Lenses from normal eyes and from eyes which had been exposed to microwaves were used. The eyes exposed to microwaves included those with totally cataractous lenses and those with lenses which contained the circumscribed, posterior cortical type of opacity. Some lenses from eyes enucleated immediately after exposure to microwaves appeared normal and others showed a diffuse subcapsular opacity associated with damage to other ocular structures.

A number of enzymes were studied in these lenses. Because little was known of enzymic activity in normal lenses, a more or less arbitrary selection of certain enzymes was made. The two main groups of enzymes which were investigated were certain L-peptidases and the phosphatases.

A study was made of the phosphatases which attack adenosine triphosphate (ATP), a compound which is widespread in living matter and which contains two phosphate radicals linked by bonds rich in energy. These bonds make readily available the energy for many chemical reactions in the body, for example, those associated with muscular contraction.

Adenosine triphosphatase, commonly called ATPase, was chosen because of its possible involvement in the transport of substances through membranes. Pyrophosphatase was chosen because it may play a role in the metabolism of ATP, inasmuch as it has been shown by Zeller[4] that at least one ATPase (ophio-ATPase) liberates pyrophosphate from ATP. L-peptidases were chosen because of the theory proposed by Krause[5] that proteolytic enzymes are involved in the formation of cataracts.

Even though the presence of adenosine triphosphatase had not been previously demonstrated in the lens, it was found that the normal lenses of rats, dogs, horses, and rabbits (table 1), and the immature cat-

aractous lenses of human beings contain this enzyme.

In addition, a pyrophosphatase of even greater activity than the adenosine triphosphatase was found in these lenses (table 2). Pyrophosphatase splits pyrophosphoric acid into two molecules of phosphoric acid (orthophosphate). This enzyme shows similar properties to the pyrophosphatases of the brain and erythrocytes.

L-peptidases, which split peptides into amino acids, were also found in the lens of the rabbit. These enzymes act on L-glycyl-leucine, L-leucyl-glycine, and L-leucyl-glycyl-glycine.

As it was necessary in all experiments to use two lenses, the procedure used to obtain and prepare them for analysis was as follows:

The rabbits were killed and the eyes were enucleated and stored for about 18 hours at about 5°C. in stoppered bottles which contained cotton moistened with physiologic saline solution. Then the lenses were carefully removed from the eyes by the following technique:

Three meridional incisions were made through the coats of the eye from the optic nerve to the limbus. The vitreous was pulled away from the posterior surface of the lens. With small scissors, the suspensory ligament was cut at its attachment to the lens, and any small pieces of pigment or of zonule were carefully removed from the equator.

TABLE 1

ADENOSINE TRIPHOSPHATASE IN LENSES FROM EYES OF NORMAL RABBITS*

Number of Experiments	Q_{AP}† Values of Adenosine Triphosphatase		
	Mean	Smallest	Highest
29	23.4±0.65‡	16	31

* ATP, 0.00125 molar; magnesium chloride, 0.00168 molar; 0.1 molar glycine buffer, pH 8.3; homogenate corresponding to 10.1 mg. of tissue; volume 0.6 ml.; incubation period, 15 minutes.

† Q_{AP} = micromoles of inorganic phosphorus per milligram of fresh tissue per hour.

‡ The figure after the ± is the standard error of the mean.

TABLE 2

PYROPHOSPHATASE IN LENSES FROM EYES OF NORMAL RABBITS*

Number of Experiments	Q_{AP}† Values of Pyrophosphatase		
	Mean	Smallest	Highest
28	113.8±6.0‡	70	178

* Pyrophosphate 0.00168 molar; magnesium chloride, 0.00234 molar; glycine buffer, pH 8.3; homogenate corresponding to 2.8 mg. of tissue; volume 0.6 ml.; incubation period, 10 minutes.

† Q_{AP} = micromoles of inorganic phosphorus for milligram of fresh tissue per hour.

‡ 6.0 is the standard error of the mean.

The lens was rolled on filter paper to remove tenacious vitreous and was immediately placed in a homogenizing tube which had already been weighed and contained exactly one ml. of 0.9-percent ice-cold saline solution. After the tube and its contents were weighed, the weight of the combined lenses was determined by finding the difference between the two weights.

A diluted solution was made of one gm. of lens to five ml. of physiologic saline and homogenized for exactly 10 minutes in a glass homogenizing tube in an ice bath. The homogenate was dialyzed for three hours in 200 ml. of cold 0.9-percent saline solution; the saline solution was changed every 30 minutes, and the dialysate was placed in the icebox and tested for enzymic activity within four hours. In the tests for peptidases, undialyzed homogenate was used.

The activity of the two phosphatases was measured by the amount of inorganic phosphate liberated from subtrate after incubation with homogenate for a given time at a fixed pH (footnotes of tables 1 and 2). To the deproteinized solution, molybdate was added, and the phosphomolybdate complex was extracted by isobutanol and reduced with stannous chloride. For details, see the report of Zeller.[6]

Activity of the L-peptidases was determined by mixing homogenate, substrate, and snake venom in a Warburg apparatus. The free L-amino acid liberated by the action of the peptidase was oxidized by the L-

amino acid oxidase in the venom. Zeller and Maritz[7] give this method in detail.

Before investigation was made of the effect of exposure of the eye to microwaves on the activity of the enzymes in the lens, a preliminary series of experiments was performed, in which the thermolability of these enzymes in homogenate of lens was tested in vitro.

It was found that, in homogenate of lens, both adenosine triphosphatase and pyrophosphatase are much more sensitive to heat than most other enzymes. Although most other enzymes are destroyed only at 60°C., the former are thermolabile at 45°C., the pyrophosphatase being much more heat labile than the adenosine triphosphatase (fig. 3).

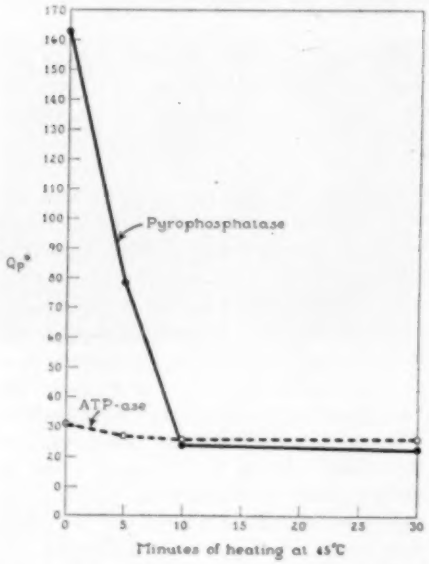

Fig. 3 (Daily, *et al.*). Heat lability of ATPase and pyrophosphatase at 45°C.

Thermolability occurs in a zone of temperature which, as mentioned before, is present in the eye during and after exposure to microwaves. Since these enzymes are heat labile in vitro, they also may be heat labile in the eye at the temperatures produced by exposure to microwaves.

Control experiments were performed in order to determine the degree of variation in the activity of the phosphatases in normal lenses of different animals. In five experiments, significant difference was not found between the activity of these enzymes in the lenses from the two eyes of the same rabbit (table 3). In 29 experiments, a fairly uniform activity of the adenosine triphosphatase was found in the lenses from the eyes of different rabbits.

Variation was apparent in the activity of pyrophosphatase in the lenses from different rabbits (table 2), possibly owing to the higher values of pyrophosphatase. If these values are reduced to the level of those of the ATPase, the standard error of the mean for pyrophosphatase is ± 1.2 which is not far from that of ± 0.65 for the ATPase.

Because of the variation in the activity of

TABLE 3

ACTIVITY OF ADENOSINE TRIPHOSPHATASE AND PYROPHOSPHATASE IN LENSES OF THE SAME ANIMAL

Experiments	Q_{PP}* Values			
	Adenosine Triphosphatase		Pyrophosphatase	
	Right	Left	Right	Left
1	26	29	152	157
2	23	21	79	84
3	24	24	100	109
4	28	23	104	106
5	21	20	71	54

* Q_{PP} = micromoles of inorganic phosphorus per milligram of fresh tissue per hour.

TABLE 4

ACTIVITY OF ADENOSINE TRIPHOSPHATASE AND OF PYROPHOSPHATASE IN LENSES OF RABBITS IMMEDIATELY AFTER EXPOSURE OF EYES TO MICROWAVES WITHOUT VISIBLE DAMAGE TO OCULAR STRUCTURES

Experiments	Q_{MP}* Values			
	Adenosine Triphosphatase		Pyrophosphatase	
	Unexposed	Exposed	Unexposed	Exposed
1	26	17	70	61
2	22	22	87	87
3	16	24	94	95
4	22	18	88	85
5	21	22	94	98
Mean Values	21.4±1.6†	20.6±1.3†	86.6±4.4†	85.2±6.5†
Difference	−0.8±2.3†		−1.4±2.2†	

* Q_{MP} = micromoles of inorganic phosphorus per milligram of fresh tissue per hour.
† The figure after the ± is the standard error of the mean. For the differences the standard error was calculated from the paired differences.

pyrophosphatase in the normal lenses of different rabbits, only one eye of each rabbit was exposed to microwaves while the other was used as a control in the following experiments. It was necessary in all experiments to combine two lenses for analysis. Consequently, in each of the following experiments one eye of each of two rabbits was exposed to microwaves.

The exposure was made at a distance of two inches from Director C to the eye with an output of 94 watts from the microwave generator for 10 minutes. Immediately after exposure, the animals were killed and the lenses were subsequently analyzed.

It was demonstrated by our data that whenever damage to the lens and other ocular structures was not grossly visible in the enucleated eyes immediately after exposure to microwaves, the activity of either the two phosphatases or the peptidases was not reduced (table 4).

When severe injury to the lens and other ocular structures was visible, however, reduction in the activity of the pyrophosphatase was decided (table 5).

The pyrophosphatase in the lens would appear, therefore, to be heat labile in vivo as well as in homogenate of lens.

In six experiments in which a circumscribed, posterior cortical type of cataract developed after a delayed interval of time following exposure to microwaves, no reduction in the activity of adenosine triphosphatase and of pyrophosphatase was found. In only one of these experiments, however, were the contralateral eyes of the same animals used as controls.

In two experiments in which totally cataractous lenses were produced by micro-

TABLE 5

REDUCTION IN ACTIVITY OF PYROPHOSPHATASE OF LENSES OF RABBITS IMMEDIATELY AFTER EXPOSURE OF EYES TO MICROWAVES WITH VISIBLE DAMAGE TO THE LENS AND OTHER OCULAR STRUCTURES

Experiments	Q_{MP}* Values of Pyrophosphatase	
	Unexposed	Exposed
1	83	45
2	162	92
3	112	54
4	140	51
5	137	91
6	150	41
7	149	72
Mean values	133.3±10.2†	63.7±8.1†
Difference	−69.6±9.4†	

* Q_{MP} = micromoles of inorganic phosphorus per milligram of fresh tissue per hour.
† The figure after the ± is the standard error of the mean. For the differences the standard error was calculated from the paired differences.

TABLE 6

ACTIVITY OF ADENOSINE TRIPHOSPHATASE AND OF PYROPHOSPHATASE IN NORMAL LENSES AND IN LENSES WITH MATURE CATARACTS PRODUCED BY MICROWAVES*

Type of Lens	Q_{ap}† Values	
	Adenosine Triphosphatase	Pyrophosphatase
Cataract	5	7
Cataract	5	20
Normal (lowest value)	16	70

* Note the marked reduction in activity of these enzymes in cataract.

† Q_{ap} = micromoles of inorganic phosphorus for milligram of fresh tissue per hour.

waves, there was practically complete loss of activity of adenosine triphosphatase and of pyrophosphatase (table 6).

Conclusions

An adenosine triphosphatase, a pyrophosphatase, and enzymes acting on L-glycyl-leucine, L-leucyl-glycine, and L-leucyl-glycyl-glycine were found in lenses from the eyes of rabbits. The adenosine triphosphatase and pyrophosphatase in homogenate of lens in vitro are much more heat labile than most enzymes, with the pyrophosphatase being more heat labile than the ATPase.

Exposure to microwaves which caused severe damage to the lens and other ocular structures greatly reduced the activity of the pyrophosphatase.

Exposures to microwaves which did not cause grossly visible damage to the eyes, did not reduce the activity of any of the enzymes studied.

Reduction in activity of adenosine triphosphatase and pyrophosphatase was not found in the circumscribed posterior cortical cataract which developed after exposure of the eye to microwaves.

Almost complete loss of activity of adenosine triphosphatase and pyrophosphatase was found in totally cataractous lenses produced by microwaves.

The Mayo Clinic.

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THE SURGICAL TREATMENT OF ESOPHORIA

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The problem of the treatment of esophoria has been a vexatious one for as long as the condition has been recognized. The present study does not attempt to provide the ultimate solution to this problem but it is felt that anything which may contribute to the comfort of these unhappy patients is worthy of reporting. Certainly a perusal of the literature on the treatment of esophoria, followed by a moment's reflection on the effect of the various methods of treatment upon one's own patients, leaves doubt as to the efficiency of many procedures.

The surgical treatment of the condition has received a minimum of attention in almost all treatises upon the subject. C. D. Townes,[1] in his excellent preliminary report upon the surgical treatment of heterophoria, seems to be the only writer who has undertaken the treatment of esophoria by surgery in any significant number of cases.

It is paradoxical that surgery in the treatment of heterotropia is widely used while surgery in heterophoria is ignored. A consideration of the etiology and physiopathology of the two conditions does not reveal why this should be so; on the contrary, surgery in the phorias should be quite successful due to the fact that at least some fusion is present in this condition which is not present in a tropia.

Scobee[2] has demonstrated the practicality of the treatment of exophoria by surgery and has tabulated excellent results. He has shown that the amount of the correction is not directly proportional to the amount of surgery but, instead, is proportional to the amount of the original deviation. Upon reflection, this opinion is found to be contrary to the older concepts of the results of surgery. My experience with exophoria has certainly borne out Scobee's conclusions. A recent communication from him suggests that he believes that the same situation prevails in esophoria.

As in the surgical treatment of exophoria, so it has been found impossible to predict accurately the amount of correction one will get with a given amount of surgery in a case of esotropia. Therefore, it seemed logical to explore the surgical treatment of esophoria.

Esophoria is that deviation of the eyes inward which is successfully held in check by fusion. The condition is quite common. Random samples of young adults showed that the average heterophoria measurement at 20 feet on the Maddox rod was about 1.5 diopters of esophoria.[3]

Low degrees of esophoria are constantly encountered but these are not associated with symptoms. It is not the purpose of this paper to argue the presence or absence of a divergence center but certainly the most logical explanation of the presence of the low degrees of esophoria found in a majority of people at 20 feet is that of an overactivity of the convergence center.

This concept would be logical in view of the fact that for any body function there must be a certain amount of reserve power to sustain adequately the use of this function for any length of time. The normal person can maintain his eyes in the reading position for long periods of time with no great fatigue. This would suggest that there must be a certain amount of convergence kept in reserve, and it is this reserve that is being elicited in heterophoria testing.

A true center for divergence has never been demonstrated anatomically nor physiologically and, therefore, the most logical assumption on the basis of the present facts would be that divergence is a passive function and that esophoria is the result of a

hypertonicity of the convergence center, while exophoria is a hypofunctioning of this same convergence center.

There is an additional factor that is often overlooked in the production of the horizontal phorias and that is the presence of various anatomic variations in the insertions of the extraocular muscles.

Scobee[4] has elucidated their function in esotropia and it may well be that they exert a similar effect in the production of esophoria. Duke-Elder,[5] in his recent publication on the subject, believes that anatomic variations do exert a marked effect in the production of esophoria.

If the conclusions just stated are true, then there is no reason for postulating the concepts of divergence excess and divergence insufficiency as a basis for the type of surgery to be done in a given case. Since it was felt that this was the true situation in the present study, the only consideration given to divergence excess or convergence insufficiency was that surgery was done on the medial rectus with hesitation if the near point of convergence was farther out than normal.

A near point of convergence of 50 mm. was taken as an arbitrary guide to the normality of this function.

Since I consider esophoria a result of dysfunction of the convergence center, abetted and sometimes overshadowed by anatomic anomalies of the medial recti, the surgical approach was invariably a recession of one or both of the medial recti unless the near point of convergence was greater than 50 mm. In the present series all of the cases had near point convergence of less than 60 mm., and all but one had a near point convergence of less than 50 mm. No consideration was given as to whether the esophoria was greater at 20 feet or 13 inches.

The symptoms associated with esophoria are so commonplace that only a brief review is necessary here. In contrast with exophoria and hyperphoria, the symptoms associated with esophoria are likely to be more or less generalized and to appear after an interval of time has elapsed following a period of close work.

The patients with esophoria will probably show poor results in depth-perception tests, as was demonstrated during the last war. They are usually rather poor golfers and tennis players and have poor safety records in industry. Frequently, esophoria is associated with a sensation of "pulling of the eyes" or of the "eyes crossing," especially after close work of any duration. Certainly the patient with any large amount of esophoria is an uncomfortable individual.

Case reports

The present study includes 15 cases of esophoria that were not relieved by the usual methods of treatment. There were eight male and seven female patients in the group, ranging in age from seven to 48 years.

The near point of convergence (determined from the bridge of the nose) was measured by means of a small light brought up toward the patient until one eye deviated. It varied from 60 mm. to almost zero when the light was practically touching the bridge of the nose, with an average of 22.8 mm.

The prism divergence at 13 inches varied from 13 to three prism diopters with an average of 7.1 diopters. It has been found that, if the prism divergence is less than 15 diopters at 13 inches, the patient almost invariably has symptoms that are not relieved by anything less than surgery.

This would seem to be borne out by the paper of Townes[1] who reported that the average prism divergence in his series of cases was 3.5 prism diopters. In a recent letter, Scobee expressed the opinion that the critical level of prism divergence at 13 inches was 12 diopters and that, if it is less than that, the patient would probably need surgery.

In this series there were five cases that had significant vertical components. Following surgery, the full residual vertical correction was corrected with vertical prisms in-

corporated into lenses. In this series, no vertical muscle surgery was found necessary.

Treatment

The refractive error was measured in all cases under a cycloplegic, atropine being used in the patients under 12 years of age, and homatropine in those over 12 years. There were four cases of myopia in the series; the remaining 11 showed hypermetropia. All patients were given a full correction for the plus error and the four myopes were given the weakest amount of minus correction that would still allow them to attain a visual acuity of 20/20.

The heterophoria measurements recorded were all made with a phorometer using a white Maddox rod and a Risley rotary prism. Screen and parallax measurements were also done in all cases but, since the correlation between the two measurements was quite close, only the Maddox-rod measurements were recorded. The rod was placed routinely over the right eye, since it has been demonstrated that there is no significant difference whether the rod is placed over the dominant or nondominant eye, unless obvious paresis is present.

The phoria measurements represent the averages of a number of different measurements since the heterophoria shows quite a tendency to vary from time to time.

As previously mentioned, all of these patients were subjected to cycloplegic refraction and were given a prescription for the correction of their refractive error. They wore this correction for a minimum of six weeks and then the heterophoria measurements were again taken and a survey of their symptoms was made.

Little more than proper correction was needed to relieve the major portion of the symptoms in many patients. The 15 in this series were not relieved by this procedure. Following this they were given a variety of treatments including a thorough explanation of their condition, orthoptics, and base-out prisms. None of these things seemed to have any effect upon the condition.

The use of thyroid[6] has been mentioned in the treatment of esophoria but I have had no experience with it and therefore cannot say whether or not it would have helped any of the patients in the series.

There are many who advocate base-out prisms; eight patients in this series were given such prisms. None of them experienced any relief from their use. In my experience, I have never seen a patient who became worse with such prisms but I do not believe that they are of any particular value. I have seen only one patient who was made comfortable by their use.

In 14 of the cases a recession of one medial rectus muscle was done and in the last a bilateral recession of the medial recti was done. In every instance the medial rectus was recessed to the region of the equator. The term "region of the equator" is used because an attempt was made in every case to recess the muscle to the equator but certainly the point of actual insertion varied a millimeter or two one way or the other from the true equator. It is believed that Prangen[7] was correct when he stated that, if surgery is necessary upon a muscle, it should be either a *full* recession or a *full* resection.

Technique of Operation

A full recession of a muscle means many things to many people. If one were to ask 10 of his colleagues what is meant by the term, he would probably get 10 different techniques. Therefore, a brief description of the technique used in this series seems in order.

All of the cases were done under general anesthesia, either ether or sodium pentothal. The conjunctiva was incised and the muscle isolated upon a Jameson muscle hook. The insertion was cleaned of the loose tissue surrounding it and a double-armed, 3-0 plain gut suture was locked in place catching several millimeters of the lateral portion of the muscle in each lock stitch.

TABLE 1

FINDINGS AND RESULTS IN 15 CASES OF ESOPHORIA

Case No.	Age	Sex	Phoria before Surgery		Recession Operation	Phoria after Surgery		Near Point of Convergence		Prism Divergence at 13"		Amount of Correction		Vertical Deviation		Anomalies Found	Postoperative Symptoms
			20 feet	13 inches		20 feet	13 inches	Before Surgery (mm.)	After Surgery (mm.)	Before Surgery (diopters)	After Surgery (diopters)	20 feet (diopters)	13 inches (diopters)	20 feet	13 inches		
1	23	M	15	22	RMR	4S*	6S	25	30	4	14	11	16	SLH	SLH	Heavy check ligaments and intermuscular membrane	Free
2	34	M	9	16	RMR	6S	6S	35	25	9	13	3	10			Heavy check ligaments	Only occasional
3	48	M	10	14	LMR	1X†	3S	15	28	3	12	11	11			None	Free
4	14	F	23	22	RMR	4S	2S	12	18	8	15	19	20			Thick intermuscular membrane; foot-plate insertion	Intermittent tropia before surgery; no symptoms after
5	7	F	27	26	LMR	7S	7S	40	35	12	17	22	19			Foot-plate insertion; thick intermuscular membrane	Free
6	13	M	18	12	LMR	1S	4X	10	15	7	13	17	13	3RH	4RH	Large muscle, many check ligaments	Free
7	21	F	6	14	LMR	4X	6X	1	10	5	12	10	20			None	Free
8	19	F	16	23	RMR	3X	10S	18	20	6	16	19	13	2RH	2RH	Extra muscle slips foot-plate insertion	Free
9	26	M	17	14	LMR	1S	1S	50	45	11	18	15	11			Thick membrane, foot-plate insertion	Free
10	31	M	12	18	LMR	0	6S	30	35	13	15	12	12			Very thick insertion heavy check ligaments	Still had headaches with close work and movies
11	18	F	14	16	RMR	6X	12X	10	15	3	16	20	28	3LH	3LH	Foot-plate insertion	No symptoms but exophoria is increasing
12	29	F	13	14	LMR	6S	9S	5	8	5	14	7	5			None	Free
13	17	F	23	32	RMR LMR	2X	4X	22	20	10	22	25	36	4LH	3LH	Rt. none; left, heavy check ligaments; foot-plate	Intermittent tropia before surgery; no symptoms after
14	37	M	8	17	RMR	2S	4S	60	55	4	13	6	13			None	Free
15	33	M	12	19	LMR	4S	4S	10	15	7	15	8	15			None	Headaches present as before surgery

* S—Esophoria in diopters
† X—Exophoria in diopters

The muscle was then freed from its insertion, cutting as close as possible to the sclera. Following this all of the check ligaments and secondary attachments of the muscle were freed posteriorly as far as possible. The intermuscular membrane was cut above and below the muscle back as far as the equator. Following these procedures the muscle should retract freely out of sight.

If it was found that all of the attachments were free, the muscle was reattached to the sclera in the region of the equator. The conjunctiva was closed with three or four interrupted gut sutures.

Anatomic anomalies that were considered significant were found in 10 (66 percent) of the cases; these are listed in Table 1. They varied from a thickening of the intermuscular membrane to secondary foot-plate types of insertions and many heavy check ligaments. The number of cases compares quite closely with that found in esotropia, and the percentage is certainly too high to be without significance.

The decision as to which muscle was to be recessed was based upon two things: (1) If the esophoria was greater with one eye fixing than with the other, it was tentatively decided to attack that eye surgically; (2) the forced-duction test was used after the patient was under deep general anesthesia and, if resistance to abduction was encountered in one eye, then that eye was attacked.

Results

On the whole the results were most gratifying. They were certainly more satisfactory than other methods that had been tried. Of course, if it is possible to relieve completely the symptoms with simpler methods, those methods should be given a thorough trial. The relief of symptoms is surely not a very reliable criterion for the evaluation of a method because it is entirely a subjective finding that may be greatly influenced by many factors other than the method under consideration.

TABLE 2

Summary of results

Average	20 feet	13 inches
	Diopters	Diopters
Esophoria preop.	15.5	18.6
Correction	13.6	16.1
Prism divergence preop.		7.1
Prism divergence postop.		15.0
NPC preop. 22.8 mm.		
NPC postop. 24.8 mm.		

Realizing this pitfall, it is still of interest to note that, of the 15 cases, all but two were essentially asymptomatic. More objective analyses revealed that the subjective findings were well substantiated.

The measurements of all of the patients were more or less normalized as can be seen from Table 1. The average esophoria prior to operation was 15.5 prism diopters at 20 feet and 18.6 prism diopters at 13 inches. Two of the patients had an intermittent esotropia. The average amount of correction obtained was 13.6 prism diopters at 20 feet and 16.1 prism diopters at 13 inches (table 2).

One fact becomes immediately apparent: The average correction was very close to the average heterophoria prior to surgery. This fact attains much greater significance when the amount of correction obtained is plotted against the original amount of heterophoria in a scatter diagram (fig. 1).

As can be readily seen the general distri-

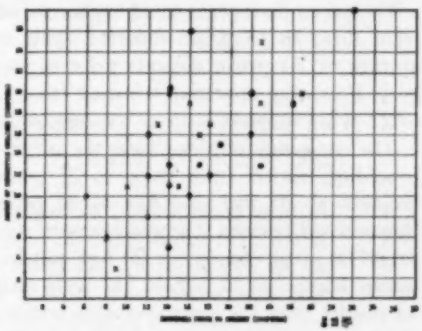

Fig. 1 (Stine). Scatter diagram, showing the amount of correction obtained plotted against the original amount of heterophoria.

bution of the dots is approximately on a line at a 45-degree angle. This makes the conclusion inescapable that the amount of correction resulting from the same operation is not proportional to the amount of surgery done but it is almost directly proportional to the amount of original deviation. The one case that had a bilateral recession stayed within the same general pattern of distribution.

This conclusion, if carried to its extreme, means that if two patients are seen, one with 20 diopters of esophoria and one with 10, and the same operation is done on both, the result would be that both would be orthophoric. Of course, this ideal condition is not always realized but the general principle seems to be true.

The near point of convergence was not significantly different before and after surgery. The average before surgery was 22.8 mm. and after surgery was 24.8 mm. This small difference is well within the limits of error of the method of measurement. This has been my experience following recession procedures done for the correction of esotropia and, although it is impossible to say at this time whether or not there will be any increase in the near point of convergence in future years, there would seem to be no reason why there should be. This is a question that time alone can answer.

The prism divergence at 13 inches varied from three to 13 prism diopters, with an average of 7.1 prism diopters prior to surgery. Following operation it varied from 12 to 22 prism diopters with an average of 15.

The correction obtained from the surgical procedure varied from three to 25 prism diopters at 20 feet and five to 36 prism diopters at 13 inches. The average correction was 13.6 prism diopters at 20 feet and 16.1 prism diopters at 13 inches. The wide range of results from the same operation makes it obvious that to attempt to calculate the effect of operation prior to surgery in terms of degrees per millimeter is almost impossible.

Case 13 is of special interest. The original deviation was 23 diopters of esophoria at 20 feet and 32 diopters at 13 inches with occasional lapses into a frank esotropia.

It was decided to attack the right medial rectus muscle but, when this was exposed, it was found to be a completely normal muscle with no sign of unusual attachments. The left medical rectus muscle was therefore exposed and was found to have a foot-plate insertion, heavy check ligaments, and a thickened intermuscular membrane superiorly.

Although a bilateral recession of the medial recti was done, it was felt that, probably recession of the left medial rectus would have been sufficient to relieve her of her symptoms. It is of interest to note that this patient was not overcorrected.

Conclusions

The results of the surgical treatment of 15 cases of esophoria with symptoms not relieved by ordinary methods are presented. It was found that the recession of one medial rectus muscle was sufficient to correct, both subjectively and objectively, moderate degrees of esophoria. It was found to be a safe procedure with only one case of overcorrection and this one not too serious.

The results show that the remarkable neuromuscular mechanism makes it possible for the surgeon to be much more bold in his surgery than was previously thought possible. The results are certainly confirmation of the statements of Prangen when he said that, if one has decided to attack a muscle, one should either recess or resect it fully; furthermore, that more poor results follow excessive timidity then temerity on the part of the surgeon.

Certainly the results of such a small number of cases do not entirely invalidate the concept of divergence insufficiency and the dangers of attacking the medial recti in such a condition but they do at least indicate that such a danger may be vastly overrated.

They would seem to confirm and expand

Scobee's concept that all heterophoria is a result of two main things: (1) A dysfunction of the convergence center and (2) the effect upon the function of the oculorotary muscles of anatomic anomalies associated with them.

It should be further pointed out that the results of the treatment of esophoria herein reported are quite similar to the results when exophoria is treated by bilateral recession of the lateral recti; that is, that the amount of the correction is proportional to the amount of the original deviation.

This whole theory can be summarized by saying that esophoria is a result of hypertonicity of the convergence center frequently encouraged by anatomic anomalies of the medial rectus muscles and that this condition can be corrected by removing the anatomic defects and decreasing the effective force of the medial rectus muscle by changing its insertion.

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Ophthalmic Miniatures

To George Whately

Passy, 21 August, 1784

. . . Your eyes must continue very good, since you can write so small a hand without spectacles. I cannot distinguish a letter, even of large print, but am happy in the invention of double spectacles, which serving for distant objects as well as near ones, make my eyes as useful to me as ever they were. If all the other defects and infirmities were as easily and cheaply remedied, it would be worth while for friends to live a great deal longer, but I look upon death to be as necessary to our constitution as sleep. We shall rise refreshed in the morning.

B. Franklin.

To Mrs. Jane Mecom

London, 13 January, 1772

Dear Sister,

. . . I doubt you have taken too old a pair of glasses, being tempted by their magnifying greatly. But people in choosing should only aim at remedying the defect. The glasses that enable them to see *as well*, at the *same distance* they used to hold their book or work, while their eyes were good, are those they should choose; not such as make them see *better*, for such contribute to hasten the time when still older glasses will become necessary. . . .

Your affectionate brother,
B. Franklin.

NOTES, CASES, INSTRUMENTS

BLEPHAROCHALASIS*

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Numerous reports on this interesting condition appeared in the literature between 1922 and 1940, especially in the foreign journals. Since that time, a thorough search does not reveal a single article and the textbooks of ophthalmology devote only a few sentences to its description. When our patient presented himself for treatment, it seemed worth-while to report his case, not only to bring blepharochalasis to the attention of the profession again, but also because of an associated skin disease.

CASE REPORT

History. M. K., a white man, aged 53 years, had difficulty in seeing due to drooping of both upper eyelids. He stated that he had had slit eyes as long as he could remember, but about 15 years ago he noticed beginning drooping of both upper lids with turning in of the eyelashes, resulting in the formation of a shadow before both eyes and impairment of vision. In 1940, he developed vitiligo which became generalized and at the present involves his entire body. There was no history of a similar eye condition in any member of the family nor any tendency to angioneurotic edema.

Fig. 1 (Titche and O'Connor). Patient before operation.

Physical examination revealed that the skin of both upper lids was loose, hung down and completely covered the lashes, especially at the outer canthi (fig. 1). The skin showed many fine wrinkles and could be picked up easily from the underlying structures. It did not fall back into place when released.

There was a loss of the superior temporal portion of both fields, but when the upper lids were elevated, the fields became normal. The skin of the entire body showed a generalized vitiligo.

Operation. Under local anesthesia, an elliptical piece of skin was excised from each upper eyelid and the skin edges approximated with interrupted sutures of silk which passed through the upper edge of the tarsus. The sutures were removed on the fourth day and healing was uneventful. The final result is shown in Figure 2. The visual fields were normal.

Pathologic study. Examination of the excised portions of skin revealed the epidermis to be thin, but intact. The basal membranes were intact. The capillaries and arterioles of the corium appeared to be somewhat increased in number, congested, and showed cuffs of inflammatory cells consisting predominantly of lymphocytes with occasional plasma cells, eosinophils, and a few polys. These cuffs of inflammatory cells were also found near the hair follicles and sebaceous glands and around the perifollicular capillaries. An abundance of sebaceous glands was seen (fig. 3).

Fig. 2 (Titche and O'Connor). Patient after operation.

DISCUSSION

Alvis[1] mentioned that blepharochalasis was described first by Beers in 1807, and the name given to the condition by Fuchs in 1896. The first American report was by Lambert in 1900. The disease usually af-

*From the Veterans Administration Hospital, Tucson, Arizona. Reviewed in the Veterans Administration and published with the approval of the chief medical director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

fects young persons between the ages of 15 and 25 years of age and does not show a predilection as far as sex is concerned. The etiology of the condition is unknown and many theories have been proposed.

Alibert,[5] in 1835, believed that it appeared in those who worked in the field and whose occupation required the head to be turned toward the ground for long periods of time. Endocrine dysfunction, angioneurotic edema, infection, sympathetic disturbances, and a congenital deficiency in the subcutaneous tissue have all been proposed.

Laffer[8] and Dejean and Viallefont[3] reported the association of blepharochalasis and double lip in their patients. Panneton[10] saw a case of blepharochalasis and, after investigation, discovered 51 members of a family of 79 had the condition in variable degrees. From this he believed that perhaps heredity plays a part in the etiology.

The onset of blepharochalasis is insidious and slowly progressive. There are attacks of swelling of the upper eyelids coming on at various intervals, each succeeding attack appearing sooner and lasting longer until the characteristic bagginess of the skin results.

Margerin and Plicque[9] reported that Fuchs described two forms of the condition. In the first, the pendant skin, wrinkled and very thin, offers an appearance which has been compared with cigarette paper. In the other, the skin also is thin with dilatation of the subcutaneous veins but is characterized by relaxation of the orbital aponeurosis which permits a herniation of the orbital contents, especially the lacrimal gland.

Panneton[10] states that there are three degrees of blepharochalasis: (1) The lid falls in a fold and the skin is edematous; (2) the anomaly is more marked, there being many horizontal folds and a scrotal appearance of the skin; (3) there is the relaxation of the orbital aponeurosis as described by Fuchs.

The pathology has been the subject of considerable discussion. All of the investigators have found an increase in the number of blood vessels with endothelial proliferation and infiltration of round cells.

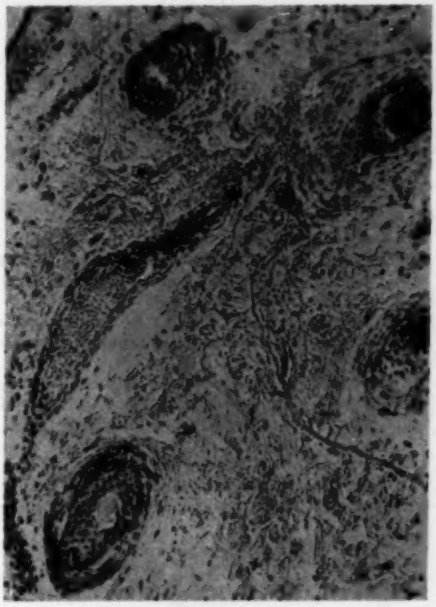

Fig. 3 (Titche and O'Connor). Photomicrograph of excised skin.

Fuchs,[6] Fehr,[5] Hollos,[7] Alvis,[1] and Dejean and Viallefont[3] found that the elastic fibers were lost or markedly atrophic. Benedict,[2] Friedenwald,[4] and Verhoeff and Friedenwald[12] found no decrease in the elastic tissue and the former stated that it was possible that the elastic fibers were slightly thinned as a result of the apparent widening of the spaces in the subcutaneous tissue.

As far as treatment is concerned, initially, Hadley[5] stated that Fuchs attempted to produce a sclerosis by injections of iodine in alcohol under the skin, but without benefit, and later advocated excision of an elliptical portion of the superfluous skin.

Benedict[2] suggested excision of the redundant skin and subcutaneous tissue with fixation of the lower margin of the wound to the upper margin of the tarsus, which is the accepted procedure at the present time. Van Lint[11] advocated this procedure, but stated that complete cure is rare, only tem-

porary relief being obtained, since the skin would become detached from the tarsus.

Summary

A case of blepharochalasis in a 53-year-old white man has been presented. There was an associated generalized vitiligo which we do not believe played a role in the etiology of this condition.

The photographs were made by Joseph E. Mineo, chief, Medical Illustration Laboratory, Veterans Administration Hospital, Tucson, Arizona.

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RAPID CLOSURE OF WOUND IN CATARACT EXTRACTION

Report of an Improved Instrument

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In cataract extraction, loss of vitreous occurs in a certain percentage of cases even when the operation is performed by an experienced surgeon using unimpeachable technique. Such an unfortunate event is often followed by slow healing, unsatisfactory end results, or other postoperative complications, sometimes of a serious nature.[1]

Loss of vitreous can usually be traced to preëxisting pathologic conditions, or to postoperative incidents, such as vomiting, coughing, straining, or injury, which may be prevented through careful nursing of the patient.

However, in the presence of such pathologic conditions as fluid vitreous, increased intraocular pressure, defective zonular fibers, dislocation of the lens, high degrees of myopia, or a large, prominent eyeball, loss of vitreous can be reduced to a minimum only through an improved operative technique.

In this respect rapid closure of the incision assumes decisive importance. It has been stated[2] that the wound should be closed within from five to 15 seconds after the lens has been delivered, especially when there is danger of loss of vitreous. The necessity of preplacing sutures has been stressed by Berens and Bogart.[3]

In a modification of the Stallard[4] procedure, Mullen[5] tied a knot to one end of the suture in order to prevent it from slipping, and achieved quick closure by pulling the other end. According to Castroviejo,[6] rapid tightening of the margins is possible by placing a slip-knot in the corneal portion of the central suture and drawing at its opposite end.

I have found that immediate closure of the incision following extraction of the lens is facilitated by a little contrivance, which also permits control of the wound edges during operation and can be used for tightening the margins at any time, should the need arise.

A tiny, well-curved hook is soldered in an oblique position to the handle of whichever instrument is selected for cataract extraction. Experience has shown that it is best to place the hook at a distance of about 15 mm. from the lower end of the handle.

For extracapsular extraction it is preferable that the hook be affixed to the handle of the lens (wire) loop—which of course is held in the left hand—rather than to the instrument used for expression; thus the hook will not obscure the operative field and the surgeon can manipulate the expressor freely with the right hand (fig. 1).

In intracapsular extraction the operator's main attention is on the intracapsular forceps or the suction disc, as the case may be, and consequently the hook is attached to the instrument held in the right hand. The little contrivance is therefore affixed to Daviel spoon, Arruga expressor, muscle hook, or to any other instrument preferred for this procedure (fig. 2).

Both ends of the central corneoscleral suture are tied together at the proper distance from their insertions, and the loop is placed on the hook. With a finger on the suture it can be kept more or less taut and the surgeon can thus adjust the width of the wound as the extraction proceeds.

When the instrument is lifted in order to deliver the lens, the same motion results automatically in tightening of the suture and the incision is immediately closed. If wing sutures are used they can now be tied, while the assistant simply holds the instrument up, keeping the central incision closed.

By cutting both arms of the central corneoscleral suture, the ends are again freed and then secured for definitive closure of the wound.

By the method described, quick closure of the corneal incision becomes possible, even though only an inexperienced assistant may be at hand. Furthermore, as temporary tightening of the margins is achieved at the very moment of delivery of the lens, the danger of extrusion of vitreous is for all practical purposes eliminated.

Fig. 1 (Tower). Well-curved hook on handle of lens loop, for extracapsular extraction. The device is placed at a distance of 15 mm. from the lower end of the handle.

Fig. 2 (Tower). Hook on handle of Daviel spoon, for intracapsular extraction.

Added advantages are that the width of the wound can be easily regulated during surgery, and that rapid and complete closure of the incision is possible in case of emergency.

The contrivance has been extensively used, and works equally well with the Stallard[4] suture, the Castroviejo[6] type of suture, and the Daily[7] suture.

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PALPEBRAL DERMATITIS

Following use of antistine eyedrops

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Introduction

The local use of antistine has been effective in relieving a number of manifestations of eye allergy. Very few reports have indicated that this drug may itself produce an allergic reaction. It seems appropriate, therefore, to report three patients who seem to have developed palpebral dermatitis due to the local use of antistine ophthalmic solution.

Bourquin[1] first reported that the instillation of antistine directly into the conjunctival sac was useful in relieving various types of conjunctivitis and scleritis.

Grant and Loeb,[2] and Schlaegel[3] studied the effect of antistine on normal human and rabbit eyes. They found the drug to be harmless when applied as a 0.5-percent or 0.75-percent buffered isotonic solution. Schlaegel[3] reported that a rare allergic reaction may be seen.

The antistine is usually used as a 0.5-percent solution in a buffered isotonic vehicle. It has been used in combination with privine.[4]

It has been of value in treating various types of conjunctivitis and conjunctival irritations, vernal catarrh, hay fever, recurrent hordeola, blepharitis, palpebral dermatitis, scleritis, nodular episcleritis, keratitis, and limbic keratoconjunctivitis.[1, 4-9]

Other antihistamine drugs have been found to be local sensitizers. It is not surprising that antistine should also sensitize the skin. Sulzberger, Baer, and Levin[10] and Strauss[11] reported eczematous contact-type dermatitis due to the application of pyribenzamine. Howell[12] reported that thephorin would be a sensitizer if used over a sizable area of body surface. Barksdale and Ellis[13] reported the development of vesicular eruptions within three to seven days after local application of unnamed antihistamine ointments.

Sherman and Cooke[14] found an exacerbation of contact dermatitis of the face and neck to be due to pyribenzamine in two patients and to antistine eyedrops in another. They demonstrated by the use of patch tests that patients may be sensitive to a number of related antihistamine drugs. Mosko and Peterson[15] reported one patient who developed severe contact dermatitis of the face after the repeated use of antistine eye drops.

Case reports

Case 1

A 38-year-old white woman, a school teacher, was studied on June 25, 1949, because of recurrent attacks of severe dermatitis of the left eyelids of two months' duration. For three weeks a similar recurrent lesion had been present on the left cheek and the right eyelids had become mildly involved.

Numerous local treatments had been used. These included boric-acid and saline compresses, olive oil and lime water, resorcinol, antistine eyedrops, and thephorin ointment. She had had several barbiturates, pyribenzamine, and benadryl orally. In addition to her eye symptoms she had mild perennial vasomotor rhinitis.

Examination showed redness, edema, and scaling of the skin of the left eyelid and the left cheek with a mild irritation of the lid margins of the right eye.

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Ninety-four patch tests were done on the back. Tests for antistine eyedrops, antistine tablets, and furniture polish were strongly positive. All others including benadryl and pyribenzamine were negative.

After the tests, she recalled that the onset of her symptoms coincided with waxing her furniture and that several exacerbations occurred after contact with wax. She also recalled that she got worse when using antistine eyedrops and that the face lesion occurred where the drops ran down from her eye. The antistine had been used for about a month when the studies were carried out.

She cleared up promptly when she avoided furniture polish and antistine.

Case 2

A 57-year-old white, retired school teacher and housewife was studied on September 9, 1949, because of dermatitis of the lids. She dated the onset of her trouble to 1930 at which time she began having recurrent attacks of conjunctivitis every 18 to 24 months. By 1948 she was having almost daily symptoms.

In July, 1948, she began using antistine eyedrops. They gave marked relief. On August 31, 1949, an acute exacerbation occurred. There was intense itching of the lids, with redness, vesicle formation, and edema. There was also an associated conjunctivitis. At that time she noted that antistine no longer gave relief. In fact her eyes improved when the drug was discontinued.

Later, when on one occasion antistine drops were put into her eyes accidentally, she definitely got worse. In addition she had also used eserine and estivin eyedrops, and had taken pyribenzamine and neo-antergan by mouth. Her general health was good. She had mild perennial vasomotor rhinitis.

Examinaiton showed the lids to be red and swollen with eczematous changes. The conjunctivas were clear.

Skin tests were done. There were several intradermal reactions to foods, inhalants, bacteria, and fungi. One hundred and six patch tests were done on the back. There were definite reactions to several soaps and to antistine eye drops. The test for estivin was negative. Tests for other antihistamine drugs were not done.

She stopped using the antistine. A report in March, 1950, indicated no further violent flareups. She continued to have occasional swelling of her lids that seemed to be associated with certain foods. She obtained relief from her perennial vasomotor rhinitis symptoms by the use of pyribenzamine. This drug did not affect her eyes.

Case 3

A 52-year-old farm wife was first seen October 17, 1949, for burning and redness of her eyes. Her symptoms began in August, 1948, with an acute attack of conjunctivitis and ulceration of the inner surface of the lids. She was immediately relieved by antistine eyedrops. In December, 1948, she had another similar episode that responded promptly to the same drops. A third similar episode began about October 7, 1949.

For this she used antistine eyedrops which produced immediate burning and itching of the lids. The next day the lids were red and the following day swollen. She continued to use the drops. In addition to the eye symptoms she also had mild perennial hay fever and seborrheic dermatitis.

Examination showed marked redness of the entire conjunctiva of both eyes with redness and weeping of the skin of the upper and lower lids.

Eighty-three patch tests were done on the back. There were several reactions to soap. All others including those to pyribenzamine and antistine were negative.

She improved promptly when she stopped using the antistine. She has not consented to patch test her lids with antistine.

Summary and Conclusions

Three patients developed severe palpebral dermatitis after using antistine ophthalmic solution. In one the symptoms developed within a month after first using the drug. In two they developed in about 13 months.

All of them had conjunctivitis or palpebral dermatitis before using the antistine but, in each case, the history indicated that the use of this preparation seemed to make the original lesion worse or more extensive.

Two of them gave patch reactions to antistine, as well as to other substances. In the patient who did not react to antistine, the history and course of her illness were so conclusive as to leave little doubt that the drug was important. It is well known that materials may not produce patch reactions unless applied directly to the site of the dermatitis.[16]

Antistine ophthalmic solution is useful for the symptomatic treatment of certain allergic and inflammatory conditions of the eyes. It may sensitize the skin or conjunctiva and therefore should be used only when definitely indicated. It should be stopped promptly if lid or conjunctival inflammation develops or becomes worse.

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CORTISONE IN GLAUCOMA SECONDARY TO UVEITIS

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The proper management of glaucoma secondary to uveitis has, up to the present time, presented a serious problem. If mydriatics are used, the tension may be increased by further blocking of the chamber angle. Miotics are quite likely to increase the inflammatory reaction and permit adhesions of the iris to the anterior lens capsule. The gravity of this situation has recently been discussed by Clark.[1]

Recent reports[2-5] of the local use of cortisone in the eye for the control of inflammatory diseases indicate that this substance may present a solution to the problem. The following case is reported to show this may be true.

Case report

A Caucasian man, aged 64 years, was examined on December 1, 1950. He had noticed blurred vision and pain in the left eye for four days; for the past two nights the pain was sufficiently severe to keep him awake. The vision in the right eye was 20/20; in the left, 20/200, with correction. There was moderate circumcorneal injection in the left eye. The cornea was steamy.

Examination with the slitlamp and corneal microscope revealed subepithelial and stromal edema of the cornea. There were deposits on the back of the cornea. The tension in the right eye was 38 mm. Hg (McLean); in the left, 70 mm. Hg.

He was admitted to Hilo Memorial Hospital. The blood pressure on admission was 220/94 mm. Hg, but this soon decreased to 160/80 mm. Hg. He weighed 136 pounds.[2] The quantitative eosinophil count was 227 per cmm. No etiologic factor was discovered.

Cortone,* full strength, was used, one drop in the eye every hour during the day

* The cortone* used in this case was the saline suspension for parenteral use prepared by Merck & Company, Inc., Rahway, New Jersey.

and every two hours at night. The pain was relieved in four hours. The tension was reduced to 55 mm. Hg (McLean) in 18 hours and 35 mm. Hg in 30 hours. When the edema disappeared, a thick layer of cells was seen on the posterior surface of the cornea.

Homatropine (two percent) was used for 18 hours to dilate the pupil. This was replaced by atropine when the tension had returned to normal. On the fifth hospital day the dosage of cortone was reduced to one drop every two hours during the day and every four hours at night.

The patient was discharged on the eighth hospital day. The weight remained stationary and the blood pressure did not increase. The eosinophil count at the time of discharge was 192 per cmm.

Cortone was continued at home every three hours while awake. On December 18th, the deposits on the back of the cornea had decreased about 75 percent. There were very few cells in the aqueous. Medication was discontinued. On December 28th, about 20 small pigmented deposits were noted on Descemet's membrane. No cells were seen in the aqueous. The vision was 20/30+, with correction.

Conclusions

1. A case of glaucoma secondary to uveitis is presented in which rapid lowering of the ocular tension took place after the local use of cortisone.

2. The use of cortisone did not affect the weight or blood pressure. The slight drop in the eosinophil count is of questionable significance.

3. Further experience is necessary to determine whether this is a specific method of treatment for this condition.

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A NEW OPHTHALMIC IRRIGATING SOLUTION*

Cetyldimethylbenzylammonium Chloride

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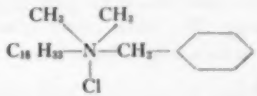
Many types of drugs have been used to irrigate the conjunctival sac prior to surgery. Some of these have been normal saline, argyrol, aqueous penicillin, 0.25-percent $ZnSO_4$, bichloride of mercury ointment (1:3,000), metaphen (1:2,500) as an irrigating solution, or systemically, sulfonamides, sulfamylon, and typhoid-H antigen.

For the past three years we have used a preparation called cetyldimethylbenzylammonium chloride (Zettyn-Winthrop) as a preoperative irrigating solution of the conjunctival sac.

This drug has the following chemical formula:



It is a white crystalline powder soluble in water, forming a clear, colorless solution, and is soluble in ethyl acetate but insoluble in acetone. Its solutions have practically no odor and have a pH of 7.2.

Preparations with low surface tension permit the antiseptic to disperse more readily into the crevices and crypts of the con-

* From the Department of Surgery, Division of Ophthalmology, University Hospitals, Western Reserve University School of Medicine. Presented before the Association for Research in Ophthalmology, East-Central Section, Cleveland, January, 1950.

junctiva, which may harbor pathogenic organisms. The surface tension of a compound indicates to a degree the penetrating power of the solution. The surface tension of Zettyn is 40.0 dynes/cm.

In addition to its low surface tension and resulting surface penetration, the detergent action Zettyn serves the purpose of removing mucous and superficial bacteria and thus exposing the underlying tissues to the germicide.

For the past three years, we have used Zettyn, in a strength of 1:10,000, as our preoperative irrigating solution of choice. The conjunctival sac was irrigated copiously in the operating room after the routine skin preparation was done.

The preparation comes from the manufacturer as a 1:5,000 solution. We place 15 cc. of such a solution in a sterile medicine glass and add 15 cc. of distilled water. The entire 30 cc. are used for the irrigation.

We attempted to correlate the use of this drug with any postoperative infection in operated eyes. Records were kept of all patients on whom Zettyn had been used preoperatively in the past three years. However, too many factors were involved to permit accurate statistical conclusions. In the few cases in which a postoperative irritation occurred, the surgeon immediately placed the patient on antibiotics. This makes it difficult to tell if any of these eyes would have gone on to endophthalmitis.

We can state, however, that there has been no known case of hypersensitivity or any allergic manifestations following the use of the drug. We have never observed an irritation which might have been caused by the drug.

Summary

Zettyn is a new and powerful bacteriostatic and bacteriocidal agent of low surface tension which has proved very successful for a preoperative irrigation of the conjunctical sac.

ANGIOID STREAKS AND PSEUDOXANTHOMA ELASTICUM*

With aneurysm of the internal carotid artery

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Cases of angioid streaks of the fundus associated with pseudoxanthoma elasticum are seen occasionally in any busy eye clinic. Pathologic studies have demonstrated elastic-tissue defects in Bruch's membrane producing the angioid streaks, and in the skin producing pseudoxanthoma elasticum.

Scheie and Freeman[1] reported biopsy studies of the ulnar artery in one of their cases in which there was a grossly thickened vessel with absence of the normal pulse. The elastic tissue in the media was fragmented and there was hyperplasia of the muscular coat.

In another of their cases, peripheral vascular disease was demonstrated clinically, and roentgenograms showed calcification of the blood vessels of the right thigh.

Retinal hemorrhages are seen frequently in patients with angioid streaks, and possibly the organization of these hemorrhages in the macula produces the lesion resembling senile disciform degeneration.

A patient with angioid streaks and pseudoxanthoma elasticum came to the eye clinic of the Cincinnati General Hospital because of the sudden onset of symptoms of a leaking aneurysm of the internal carotid artery. This complication has not been reported previously; however, its occurrence should not be surprising in view of the known generalized elastic tissue disease, including the large vessels.

Report of case

History. A 29-year-old Negress first came to the eye clinic on December 21, 1949, because of the sudden onset, three days pre-

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viously, of right-sided headache and ptosis. At that examination the patient had angioid streaks, many drusen of the fundi, and pseudoxanthoma elasticum.

Eye examination. There was a partial right ptosis, and uncorrected vision was: right eye, 20/30; left eye, 20/20. Ocular motility was normal.

When next seen, 16 days later, she had developed almost total paralysis of the right oculomotor and abducens nerves and the headache was more severe. An aneurysm of the circle of Willis was suspected and the patient was admitted to the hospital on the neurology service.

Laboratory examinations. The spinal fluid pressure, cell count, and Wassermann test were normal. The blood count, Kahn test, and urinalysis were normal. Blood pressure was 120 mm. Hg, systolic; 90 mm. Hg, diastolic; and routine physical examination was negative except for obesity.

The neurosurgical service did an open angiogram which demonstrated a 2.0 by 1.5 cm. subclinoid aneurysm in the upper end of the right internal carotid artery at the point of its entrance into the intracranial cavity. With proper precautions, the neurosurgical resident occluded the right internal carotid artery by a tantalum band. The patient remained free of ill effects.

One week later when she had recovered from the first procedure, a right frontal flap was turned, the circle of Willis exposed, and a silver clip placed on the peripheral end of the internal carotid artery. A week later the external carotid artery was occluded as a safety measure. From the time the internal carotid artery was first occluded, there was progressive improvement in the ophthalmoplegia, and six weeks later recovery appeared to be complete.

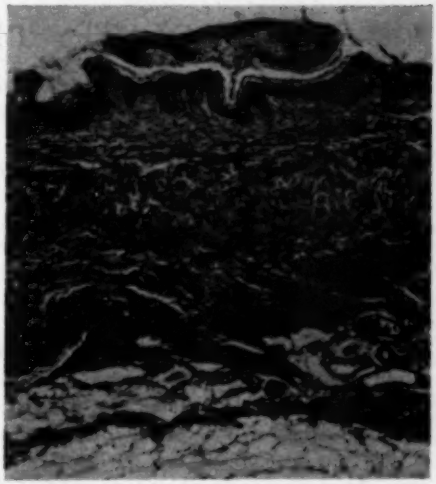

Fig. 1 (Dixon). Elastic tissue degeneration in the deep cutis of skin lesion from the axilla. Verhoeff's elastic stain.

The patient refused additional studies except skin biopsy, left the hospital against advice, and returned to her family in another state. Follow-up studies and information about her relatives have not been obtainable.

Comment. The vascular component of pseudoxanthoma elasticum with angioid streaks should be kept in mind and, as pointed out by Scheie and Freeman,[1] it is possible for vascular lesions to be its only manifestation.

903 South 21st Street.

Reference

1. Scheie, H. G., and Freeman, N. F.: Vascular disease associated with angioid streaks of the retina and pseudoxanthoma elasticum. Arch. Ophth., 35:241, 1946.

SOCIETY PROCEEDINGS

Edited by DONALD J. LYLE, M.D.

NEW YORK SOCIETY FOR CLINICAL OPHTHALMOLOGY

October 2, 1950

DR. SAMUEL GARTNER, *president*

VON HELMHOLTZ, HIS LIFE AND TIMES

DR. SOLOMON SILVER said that Hermann Ludwig von Helmholtz was born at Potsdam on August 31, 1821, the son of Ferdinand, a teacher of philology and philosophy in the German equivalent of our junior college. At a very early age he demonstrated remarkable mathematical gifts and desired to train himself in physics, then a relatively new science. Financial difficulties forced him to study medicine, a field in which his parents thought he could more easily support himself. Even this could only be accomplished by registering as a student in the Prussian Army medical course in Berlin and agreeing to serve eight years as an army surgeon after graduation.

He graduated in medicine in 1842 and published his first scientific paper in that year in which he demonstrated for the first time that nerve fibers were actually processes of nerve cells. He came under the influence of Johannes Müller, the physiologist, and Gustav Magnis, the physicist at Berlin. His short paper, "Die Erhaltung der Kraft," in 1847, laid the basis for our present concepts of the conservation of energy and was one of the greatest intellectual achievements of all time.

He became professor of physiology and general pathology at Koenigsberg in 1849 and established for the first time the rate of transmission of nervous impulses.

In 1850, he invented the ophthalmoscope and started ophthalmology on a new course. He did pioneer work on color and color vision, the mechanisms of binocular vision, and accommodation. During his Koenigsberg stay, he made his famous contributions to acoustics and hearing and, in 1863, published his classic study, "The sensation of tone as the physiological basis of music."

No summary can present the magnitude and genius of this self-trained physicist and mathematician who enriched so many fields and to whom ophthalmology owes so much.

OPHTHALMOSCOPE, ITS DEVELOPMENT AND PRESENT STATUS

DR. BERNARD FREAD gave a detailed history of the development of the ophthalmoscope and he illustrated his talk with lantern slides showing many of the older instruments and all of the contemporary ophthalmoscopes.

Dr. Fread mentioned that, in 1847, Babbage was said to have invented the ophthalmoscope, but the first practical instrument was made by Helmholtz in 1850. He used four plates of glass. In rapid succession, instrument after instrument was perfected, mirrors and prisms were used, and Rekos added the revolving disc with lenses. A new era was opened in ophthalmology and the term "amaurosis" was used less and less, as detachment of the retina, glaucoma, retinopathy, and various other diseases of the back of the eye were discovered.

CLINICAL AND PATHOLOGIC CORRELATIONS IN FUNDUS DISEASES

DR. SAMUEL GARTNER said that, when we look through the ophthalmoscope, we try to interpret what we see in terms of pathology, and describe hemorrhages, exudates, atrophy, and so forth. Though we see a good deal with the ophthalmoscope, we are limited to a low magnification of transparent tissue. Only when there is a change in color or density of the lesion do we appreciate that something has occurred. It is no wonder that

ophthalmoscopic diagnosis is often difficult and has many pitfalls.

The retina is frequently described as one organ. Actually it has compressed into it the peripheral sensory organ of vision and three neurons and nerve fibers. Retinal disease is selective, and we can be certain that not only are there anatomic and functional differences in the various neuron and nerve-fiber layers, but there are different susceptibilities to disease and degeneration. The study of the separate diseases of each layer has been scanty. It is very difficult, since it requires special study and fortunate specimens in the early stages of disease.

Dr. Gartner showed a slide demonstrating closure of the central retinal artery. The anterior layers, especially the ganglion-cell layer and the nerve-fiber layer, had atrophied. An interesting feature was that the rods and cones and the pigment epithelium were apparently intact, though of course unable to transmit light sensation since the ganglion-cell layer was gone. The nutrition from the choriocapillaris was apparently sufficient to maintain them. Central retinal artery closure was followed by the usual sequelae which included atrophy of the nerve-fiber layer, so the medullated nerves disappeared.

In Tay-Sachs's disease, a fundus picture is produced that has some similarities to closure of the central retinal artery. There is a development of a white zone about the macula with a cherry-red center, but the mechanism is different. The ganglion cells undergo a fatty degeneration and give the white appearance where they are heaped about the macula.

A typical field study in a case of multiple sclerosis shows involvement of the central and paracentral fields. The usual ophthalmoscopic examination shows no change in the retina and pallor of the temporal portion of the disc. In a man who died, at the age of 36 years, of multiple sclerosis, the ganglion cells and the nerve-fiber layer at the macular zone showed considerable atrophy.

Dr. Gartner then presented a series of slides of a man, who died at the age of 40 years. He had a moderately advanced case of retinitis pigmentosa and his retina demonstrated the disease in various stages. Dr. Gartner said that, as the disease progresses from the middle zone toward the periphery and toward the center, we can consider that the border between normal and diseased retina is the area that shows the earliest stages of the disease.

There is a relationship between degeneration of rods and cones and that of the pigment epithelium. The rods and cones need to be in contact with pigment epithelium to function properly as demonstrated in retinal detachment. There is also an association in degeneration. When the rods and cones die, the pigment epithelium also degenerates and wanders into the retina. The ganglion cells are well preserved for a very long time and are only affected very late, long after the loss of function. Further proof of this is found in the optic nerve which only shows a slight amount of atrophy at the time that the rods and cones and external nuclear layer show advanced degeneration over a large portion of the retina.

The pale waxy disc, typical of this disease, has been called atrophic. Actually there is only a small amount of atrophy till very late in the disease.

Discussion. Dr. Adalbert Fuchs opened the discussion by emphasizing the practical side of the histopathology which enables us to get a better diagnosis and therapy. Dr. Fuchs showed a picture of retinitis diabetica, in which a vessel looks something like an aneurysm surrounded by clusters of exudate. Cases of fat embolism in the retina, pseudotumor caused by an iron splinter in the retina, and pseudoretinochoroiditis centralis caused by drusen, demonstrate the importance of checking the ophthalmoscopic findings and their interpretation by pathologic study.

Bernard Kronenberg,
Recording Secretary.

COLLEGE OF PHYSICIANS OF PHILADELPHIA

Section on Ophthalmology

October 19, 1950

Dr. Wilfred Fry, *chairman*

Replacement of skin graft by basal-cell carinoma

Dr. Edmund B. Spaeth presented the case of a 60-year-old cook, who was admitted to the ward of the Graduate Hospital of the University of Pennsylvania, in 1947, with extensive keloidal cicatrix of the upper and lower lids, into the forehead, and over the bridge of the nose, resulting from a third-degree burn from hot fat. The acute traumatism occurred six months prior to this admission. The eyeball itself was in good condition.

The surgery carried out at that time consisted of scar resections and two free skin grafts. The patient was discharged from the Graduate Hospital with the lids held in median tarsorrhaphy. After his discharge, he failed to appear for any follow-up observation.

Three years later, the patient reported to the Wills Eye Hospital. A large ulcerating lesion of the upper and the lower lids at the site of the first cicatrix, extending into the forehead and over the bridge of the nose, now entirely replaced the free skin grafts. It seemed as if the grafts had undergone a complete change into a basal-cell carcinoma.

A recurrence of carcinoma at an operative site where a free skin graft had been used for partial correction is not an uncommon finding, unfortunately. When this situation occurs, the recurring malignancy pushes the graft to one side. The graft itself does not become invaded by the recurring malignancy; nor does it undergo carcinomatous transformation.

A second case was presented to illustrate this usual sequence of events. At the time of the first surgery, the scar resections and skin grafts were not examined histologically for malignancy. There seemed to be no reason for this examination.

The resections done at the time of readmission showed that the malignancy extended into the depths of the orbit to such an extent that enucleation and exenteration of the orbit was necessary. The surgery was completed by additional skin grafting after some X-ray therapy.

The first case seems to suggest a rather unusual fate for an autogenous skin graft, that is a carcinomatous transformation of the graft. One might suspect that some malignancy, undiagnosed but present, had existed prior to the original plastic surgery. This is possible considering the cause for the original burn, a suspicious carcinogenic agent—hot fat. While that is only a conjecture, it does make it impossible to state conclusively that the skin graft did undergo carcinomatous changes.

ACTH and cortisone in ophthalmology

Dr. Harold G. Scheie and (by invitation) Dr. George Tyner and Dr. John Buessler reported preliminary clinical observations on the use of ACTH and cortisone administered systematically and locally in the treatment of a variety of ocular lesions. Cortisone and ACTH seem to have an identical clinical effect upon ocular disease. The mechanism of action of these hormones is not yet known, but they apparently block response to various types of allergens and anaphylactic reactions, as well as the effects of inflammation and some chemical irritants. The underlying allergic state was unaffected, however, and persisted unchanged following withdrawal of treatment.

Both hormones can be used systemically, but since ACTH must stimulate the adrenal cortex to be effective, it cannot be used topically. Cortisone, on the other hand, can be so employed since it is an end-product. One cc. of cortisone suspension, which contains 25 mg. of the drug, was diluted with five cc. of physiologic saline solution. In the

acute stage of an ocular disease, one drop was used every one to two hours while awake.

Results observed in treating a wide variety of lesions in 55 eyes (36 patients) by cortisone of ACTH administered systemically, and 69 eyes by cortisone administered locally in the form of drops were presented.

Systemic therapy with these hormones was best suited for acute lesions which tend to run a self-limited course. This was true because ACTH and cortisone could be administered systemically for only a short period of time because of the danger of undesirable physiologic side effects which might have been induced.

Cortisone given locally was effective only in the treatment of anterior-segment lesions. Its advantage was that it could be administered over a long period of time. In our experience, the use of cortisone in the form of drops seems a safe procedure.

Cortisone and ACTH given systemically offer encouraging results in the treatment of acute focal choroiditis and endophthalmitis phacoanaphylactica. Somewhat encouraging results were obtained in the treatment of acute nongranulomatous uveitis and interstitial keratitis. More questionable benefit was obtained in the treatment of retrolental fibroplasia, optic and retrobulbar neuritis, and postoperatively following keratoplasty.

Evaluation of the response of these conditions was extremely difficult. For example, interstitial keratitis followed a notoriously unpredictable course as did retrobulbar and optic neuritis. Spontaneous arrest of the disease is likewise known to occur with retrolental fibroplasia. Further conclusion must await the accumulation of further data reported by many different observers. No improvement was noticed in the treatment of chronic granulomatous uveitis, Harada's disease, angiospastic retinopathy, Tay-Sach's disease, or thyrotropic exophthalmos.

Encouraging results with local therapy were observed in the treatment of acute nongranulomatous anterior uveitis, endophthalmitis phacoanaphylactica, iritis due to retained lens material following attempted intracapsular cataract extraction, luetic interstitial keratitis, sclerosing keratitis, superficial punctate keratitis, marginal keratitis, chronic keratoconjunctivitis due to bacterial allergy, phlyctenular keratoconjunctivitis, atypical vernal conjunctivitis (allergic), and episcleritis.

Questionable, but slightly encouraging, results were found in the treatment of keratitis, secondary uveitis, keratitis profunda, keratitis metaherpetica, and reactions following keratoplasty.

Local therapy was ineffective in the treatment of posterior uveitis of any type, mustard-gas keratitis, and Stevens-Johnson's disease.

Cortisone and ACTH

Dr. Arno E. Town and Dr. A. E. Rakoff reported a total of 29 patients who had been treated with ACTH and/or cortisone. When cortisone is administered locally, one-percent methyl-cellulose solution is used as the diluent, as it seems to have better adhesive qualities.

Inflammatory processes in the anterior segment of the eye have shown improvement. Inflammatory conditions in the posterior segment have shown no lasting improvement. Degenerative and noninflammatory diseases have not been influenced by these new hormonal substances. Because of the nature of the disease, we cannot accurately evaluate results obtained in the treatment of retrolental fibroplasia.

The real mechanism of how these drugs alter the response of tissues is unknown. Possibly Dr. Woods's theory, that in inflammatory lesions the mechanism may be the blocking or altering of the allergic response of the tissues, comes close to the answer.

Local and systemic cortisone

Dr. Irving H. Leopold, Dr. P. Robb McDonald, and (by invitation) Dr. James E.

PURNELL, DR. EDWARD J. CANNON, and DR. CHARLES G. STEINMETZ reported on the treatment of 142 eyes with local and systemic cortisone; 121 eyes were treated with subconjunctival injections of 0.5 cc. (1.25 mg.) of cortisone. Other methods of administration were the topical application of a suspension of 1.0 cc. of cortisone in 4.0 or 8.0 cc. of normal saline, the retrobulbar injection of 50 mg. of cortisone, and systemic therapy starting with 300 mg. the first day, 200 mg. the second day, and 100 mg. a day thereafter.

This paper was published in the JOURNAL, **34**:361-371 (Mar.) 1951.

Discussion. Dr. Joseph V. Klauder: It occurs to me that the three essayists who report somewhat conflicting results in treatment of acute interstitial keratitis with cortisone and ACTH may not have treated patients with a comparable degree of severity of interstitial keratitis.

As you know and as I discussed elsewhere (Am. J. Syph. Gonor. & Ven. Dis., **3**:575-599, 1947), there is considerable variation in the severity of interstitial keratitis and difficulty in evaluating therapeusis of a few patients treated. Not only is there variation in the severity of the disease but therapeutic results show a relationship to when treatment is started in the so to speak "coming out" stage of the disease process or in the receding stage.

More recently, in evaluating therapy, I graded interstitial keratitis into severe, moderate, and mild. As reported, I purposely withheld specific means of therapy in some mild cases, employing only ophthalmic treatment, and observed favorable progress of the disease with improving visual acuity.

The real problem of treatment essentially concerns severe cases.

I purposely selected for ACTH and also for cortisone therapy, full-blown, severe cases. After one week of ACTH therapy as the sole means of treatment, except the use of a mydriatic, there was no striking change in the case of three patients treated. Their considerably reduced visual acuity was about the same, the degree of opacity of the entire cornea was not appreciably changed, the iris could not be seen, the ciliary congestion was not less, nor were subjective symptoms. These patients received one or the other of the following doses of ACTH given in the course of from seven to 10 days—500 mg., 600 mg., and 700 mg.

In all patients there was a reduction in the eosinophil count. The count was not maintained at zero as Dr. Rakoff suggested by an increase in the dose of ACTH. As an additional evidence of the systemic effect of ACTH, one patient developed the so-called "moon" face, his appetite considerably improved, and he gained weight.

Since this lack of favorable response to treatment was in contrast to the results usual after one week of fever therapy, it was not considered fair to the patient to continue with ACTH and to withhold fever.

Four patients have been treated by subconjunctival injection of cortisone as detailed by Dr. Leopold and his collaborators. Not included in their report was one patient who received systemic treatment for one week in addition to local injections. During the time of cortisone therapy, no other systemic treatment was administered. In patients with bilateral involvement only one eye was treated. No striking improvement was observed from this therapy; at the most there was some difference of opinion as to an appreciable improvement. As with ACTH therapy it was not regarded as fair to the patient to continue cortisone when fever, and other glandular treatment which we are now studying, gave more promising results.

Dr. Harvey E. Thorpe: I was very much impressed by the excellent presentations of Dr. Scheie, Dr. Towne, and Dr. McDonald. In Pittsburgh, our clinical experience with ACTH and cortisone began in February, 1950.

Our first patient was a young woman with bilateral secondary glaucoma due to severe plastic cyclitis of 10 months' standing. The

etiology was not determined in spite of extensive investigation. The cyclitis and glaucoma improved with intramuscular injections of ACTH given in 25 mg. doses every six hours (100 mg./day) for three weeks. The dosage of ACTH was gradually tapered off in the second and third weeks to 20 mg. per day.

The uveitis recurred when ACTH treatment was discontinued. Resumption of ACTH was followed by temporary improvement. The inflammatory process was finally controlled with temporary restoration of vision. However, both eyes developed glaucoma in spite of surgery, and both eyes deteriorated.

Our second patient, seen in February, 1950, had a painful, severe traumatic hypopyon keratitis of two weeks' duration which had not responded to intensive treatment with aureomycin, penicillin, and sulfadiazine combined with foreign-protein therapy. Vision in his left eye was limited to light perception. The fundus could not be seen.

The response to ACTH therapy was dramatic. Pain was relieved seven hours after the patient had received 40 mg. ACTH. The keratitis and hypopyon cleared in 40 hours. The vitreous cleared sufficiently in six days so that the fundus could be photographed. At the end of two weeks' treatment, vision had returned to 20/30. When ACTH was discontinued, inflammation recurred. Resumption of ACTH treatment resulted in further improvement.

The third case was that of a patient with extensive exudative chorioretinitis. There were four large exudative lesions in the upper temporal quadrant of the right eye with extensive retinal edema and vitreous exudate. With ACTH therapy, 100 mg. per day for the first few days and the dosage gradually tapered off over a period of two more weeks, the chorioretinal lesions healed —two of them entirely without any trace and the others with later pigment proliferation.

A number of cases of acute iritis, cyclitis, and exudative choroiditis were thus treated with ACTH parenterally. Failure of an inflammatory case to respond to other therapy was an indication to try ACTH or cortisone. The improvement response was often dramatic.

A number of cases of ocular trauma with inflammation were treated with ACTH parenterally. Several were treated with cortisone parenterally. Some with sole anterior-segment involvement were given cortisone eye drops or ointment. Improvement and resolution of the process occurred in the great majority of cases, with only occasional relapse.

The Thorne test of the eosinophil response was used to determine whether ACTH should be tried or parenteral cortisone injections resorted to in severe acute cases and in cases of posterior global involvement. We found that in some instances continued large doses of ACTH were required to maintain as eosinophil drop or to maintain clinical improvement. In such instances we found it advisable to use cortisone in addition to ACTH. Using parenteral cortisone injections alone for an extended period may cause severe adrenocortical depression.

One must be careful to note that there may be variation in eosinophil response to different batches of ACTH. If a patient does not respond with a positive Thorne test to one batch of ACTH, a second batch of ACTH should be tested.

Among our series, several cases of secondary glaucoma due to uveitis or iritis responded well to ACTH and to cortisone therapy with subsidence of tension.

A case of sympathetic ophthalmia of five months' duration responded well to ACTH. The endothelial surface of the cornea was carpeted with conglomerate exudate deposits when the patient was first seen, so that one could hardly differentiate between individual keratic precipitates. No iris details could be made out. There was a secondary glaucoma.

Two days after beginning ACTH (100 mg./day divided dosage), iris details could be discerned. Interestingly enough, the secondary glaucoma was controlled only when the dosage was kept high at 80 mg. of ACTH per day. The glaucoma would recur with dose reduction, and so would the keratic precipitates. Parenteral cortisone was added to the regimen and, after a few weeks on combined ACTH and cortisone therapy, the eye became completely quiet. It was then possible to perform a cataract extraction.

This was extremely difficult, due to dense matting down of the uveal tissues to the lens. It was necessary to dissect the lens out with scissors. However, the postoperative course was uneventful. The patient was able to count fingers at the end of his convalescence, whereas he previously only had light perception.

We have concluded, after observing the clinical course of some 60 cases of ocular inflammation and trauma, that the parenteral use of ACTH or cortisone is indicated for deep and severe inflammation. On the other hand, cortisone used locally in milder anterior-segment cases ameliorates the inflammatory response of ocular tissue to irritants.

One must note that the etiologic factor is not affected by this hormone treatment and that one often must add specific treatment and remove foci of infection. However, one can now definitely state that these new hormones are a decided addition to our armamentarium in the management of ocular inflammation.

Dr. Harold G. Scheie: Dr. Klauder has quite properly emphasized the difficulty in evaluating the response of interstitial keratitis to any type of treatment because of the unpredictable course which the disease runs. The eyes, which we found responded well, showed only early involvement and, as a result, the severity of the disease could not be predicted. In the eyes which did not respond to treatment, the condition was much more advanced, showing in addition to corneal infiltrate, a heavy "salmon type" of vascularization, the disease appearing extremely severe. The second eye developed a similar involvement even after ACTH had been given systemically in treating the first eye.

Dr. Rakoff has raised an interesting point in mentioning the possibility of potassium deficiency as a cause of cataract. One of our patients treated with ACTH for uveitis, rapidly developed an intumescent cataract in a lens that was previously clear. This occurred over a period of approximately two weeks. It was impossible to ascertain whether or not a potassium deficiency due to ACTH was a contributing cause.

The papers by Dr. Town and Dr. McDonald were very enjoyable, as were Dr. Rakoff's comments. We have some experimental work under way at the university, results of which are as yet inconclusive. Some of the preliminary results parallel those of Dr. McDonald and Dr. Leopold, particularly with regard to wound healing and corneal epithelization.

Dr. Arno Town: I think that the field has been covered as well as it can be at this time. There certainly is a great deal yet to be learned about the use of ACTH and cortisone. I enjoyed Dr. Thorpe's remarks very much, and I am glad to see him here.

Dr. A. E. Rakoff: The only additional point I would like to raise is the question of initial dosage. Is it better in these cases to start with a large dose and reduce the dosage as apparently some of the men have done, or is it better to start with a small dose and build up? Our own experience leads us to believe the second method is better, because when ACTH is first started the adrenal gland is quite responsive, as indicated by eosinophil response, but naturally after a long period of stimulation the adrenal requires larger amounts of ACTH to maintain a high level of cortisone production.

Dr. P. Robb McDonald: There is one thing I would like to add. Our studies were essentially concerned with the local administration of cortisone. Many laboratory studies were carried out and none of the systemic

manifestations—retention of sodium, excretion of potassium or decrease in the eosinophils—was noted. Apparently one can get a response from the local use of cortisone independent of the general systemic effect. For this reason the local use of cortisone is of a distinct advantage.

M. Luther Kauffman,
Clerk.

COLORADO OPHTHALMOLOGICAL SOCIETY

May 20, 1950

Dr. Whitney Porter, *president*

Pigmented iris lesion

Lieut. Col. Ralph Cleveland of Fitzsimons General Hospital presented a 24-year-old white woman who had a mass on the right iris of four years' duration. This was noted at the time of a general physical examination.

The patient stated that there had been what she thought was a spot of pigment there for some time before that. The lesion was elevated, dark, and with a rough surface and did not transilluminate. The patient stated that the lesion had not changed in appearance in the past four years.

The iris was freely movable with the pupil dilating full and regularly. Dr. George A. Filmer suggested photographs with careful measurement and observation for progress of the lesion. This met with the approval of all who had seen this case.

Macular hemorrhage

Dr. Edward Swets presented a 20-year-old man whom he had first seen on April 21, 1950. The patient complained of "red vision" in the left eye when in the sun or a bright light. This had been going on for six weeks. A blow to the temple in a boxing match preceded the symptoms by 24 hours.

Examination showed a hemorrhage over the left macula. No retinal details were visible. Six days later a choroidal tear could be seen nasal to the hemorrhage. This tear was crossed by a retinal vessel which had a brushlike filamentous ending as it disappeared behind the hemorrhage. It was felt that this vessel was the source of hemorrhage.

Vision was 20/200 and the field showed a central scotoma. The right eye was normal.

Diabetic retinitis and subhyaloid hemorrhage

Dr. H. Cowan, assistant resident in ophthalmology at the University of Colorado Medical Center, presented a 57-year-old woman, a diabetic, whose disease was complicated by hypertensive cardiovascular disease. This patient had been on insulin for the past 10 years.

The blood Wassermann was positive; the Eagle test, negative. Fasting blood sugar was about 190 mg. percent; blood pressure 180/95 mm. Hg. Vision was R.E., 20/60; L.E., 20/25.

Each lens showed mild nuclear sclerosis with peripheral spokes. The left fundus showed only a Grade-1 arteriosclerosis. The right fundus showed a typical diabetic retinitis with a large recent subhyaloid hemorrhage inferiorly and changes of retinitis proliferans in the macular area. Rutin had been used in this case with indifferent result.

Dr. James Lamme of Walsenburg, Colorado, stated that he has used rutin in many cases like this one and has found that, if nothing else, it gives a sense of well being. For this reason he has used rutin as pre- and postoperative medication in other types of cases and feels that it is a valuable addition to the ophthalmologist's armamentarium.

After dinner Dr. George Stine of Colorado Springs gave a paper and demonstration of his "Rotating cross and cross cylinder test for astigmatism."

Thomas M. Van Bergen,
Recorder.

AMERICAN JOURNAL OF OPHTHALMOLOGY

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GRAEFE-KNIFE VERSUS KERATOME-SCISSORS INCISION FOR CATARACT

A discussion of the Graefe-knife incision versus the keratome-scissors incision for cataract surgery at the recent meeting of the American Ophthalmological Society has led to the following speculation as to the cause for the increasing acceptance of the keratome-scissors incision for cataract surgery.

In the past the ability to make a good Graefe incision was looked upon as the mark of a competent eye surgeon and the man who strove to be a good surgeon often boasted of his ability with the knife. To acquire this skill required a good deal of practice and training and the continued opportunity to do the incision regularly so as not to lose the touch. One European ophthalmologist stated that it was necessary for the ophthalmic surgeon to ruin "a hat-full of eyes" before he became a cataract surgeon. In addition, the old dictum, "as the incision goes, so goes the operation," was to a large extent true.

In the past, eye surgery was done in relatively few larger centers. This was the result of the fact that there were very few centers in this country where a young physician could obtain training in ophthalmology and especially in ophthalmic surgery.

The result was that many men obtained their training in ophthalmology abroad especially in Vienna. Here the training in surgery, except in the few cases where for one reason or another the candidate had an unusual entree, was obtained by taking the course in cataract surgery given by the "diener" in the clinic, who obtained pig eyes for the students to operate upon. These men then, often having obtained good training in other fields, had never operated upon a human eye.

Another group of men who had been in general practice for a varying number of years took short courses of from three to six months in so-called eye, ear, nose, and throat colleges and came home to start again as eye, ear, nose, and throat specialists.

Most of these men soon recognized their inability to do competent cataract surgery and, therefore, especially in the smaller communities, sent their cataract patients to the larger centers. Thus the men doing successful cataract surgery were fed cases from other communities which helped to keep up their skill by constant practice. They, therefore, did not lose "the touch" of the Graefe-knife incision. If a man did do his own cataract surgery and only did a small number of cases, he would often go to the slaughter house the day before surgery and obtain a dozen or more pigs' eyes in order to be able to practice the incision the night before the operation.

Even under these conditions the frequent operator at times made a bad incision and the occasional operator approached the incision with apprehension and not infrequently made a poor incision. The frequent, skilled operator, however, did and still does make many incisions without difficulty.

In the last 20 years, there has been a marked change in the training of ophthalmologists. The days of the "six weeks' specialist" are gone, due, to a great extent, to the influence of the American Board of Ophthalmology. In addition, the number of men obtaining their training abroad is very small.

Training now is obtained in institutions where surgery is taught and where the resident has an opportunity of learning to operate on patients. Many of the men who depend upon a preceptorship for their training also have opportunity for surgical training.

There has probably been little or no increase in the number of cataracts per thousand in the general population while there has been a definite increase in the number of men who have had training of one type or another in surgery. Thus there is less tendency for the cataract patients to be sent to large centers for their surgery, and therefore there is a much greater number of occasional operators.

Anyone who has watched residents do their first cataract incision with a Graefe knife and keratome-scissors must admit that the average resident approached his first Graefe with fear and trembling even though he had done a good many pigs' eye incisions preceding this. On the other hand, the resident doing his first cataract and using the keratome-scissors incision has little or no fear. While there can be difficulty with the keratome-scissors incision, the chances are less than in the Graefe incision, and certainly for the properly trained occasional operator there is less of a mental hazard.

Very few operators were willing to admit they had any difficulty with a Graefe incision until O'Brien, a very skilful Graefe-knife operator, came out with his work on the keratome-scissors incision. This has led to the increasing adoption of the method all over the country, particularly by the younger men, even in some clinics where the chief uses only the Graefe knife.

Many of the younger men have never made a Graefe-knife incision, which is undesirable as there are times when it certainly is the method of choice.

While the keratome-scissors incision would appear to be the incision of choice for the properly trained occasional operator, it does require skill. The apparent ease of the incision has led many an incompetent operator to attempt cataract surgery with disastrous results.

From observation and personal experience with both methods, it is apparent that the results in competent hands are comparable and, as was pointed out in the discussion at the meeting of the American Ophthalmological Society, it is the skill and competence of the operator rather than the type of incision that are the determining factors in the result.

With the increase of men doing surgery as the result of the newer methods of training ophthalmologists, it would seem that the time has come when some thought should be given to the possibility of designating those qualified to do eye surgery, especially intraocular surgery. The establishment of a certificate in ophthalmic surgery after an examination which included determination of the candidate's ability, as based on actual observation of his technical skill in the operating room as well as his surgical judgment, by some organization such as the American College of Surgeons would be a great step forward in the field of ophthalmic surgery.

Frederick C. Cordes.

PRIMARY VERSUS SECONDARY OPTIC ATROPHY

It is common to hear heated and anxious discussions among medical undergraduates and candidates for the "Board," regarding the characteristics which distinguish primary from secondary optic atrophy. Such discussions often are academic and may in no way reflect a true understanding of what the picture presented in the fundus actually represents. Some magic significance seems to be applied by the examinee to the ability to distinguish between the primary and secondary conditions. Indeed, not all the examiners are free of this fault. We, as teachers, and the textbooks we have written or recommend for reading, largely are responsible for this situation. A strong plea is made here for the dropping of these terms from the standard texts, and for bringing our teaching up-to-date.

The origin of the words primary and secondary optic atrophy are lost in medical antiquity. Certainly they must postdate the invention of the ophthalmoscope. And just as certainly they must antedate the development of the Wassermann test.

In the period so delineated one easily can understand the importance with which these two conditions were clothed. Many patients with optic atrophy must have been seen who had no proven lues nor any neurologic sign to help one to make the diagnosis. Thus, the origin of the term primary is understandable and it served a useful purpose.

The secondary form of atrophy naturally would have this name since it was found to follow upon papilledema or papillitis.

However, today, with our greater diagnostic facilities, the terms become much less meaningful and are even confusing. We now know that all cases are etiologically secondary. Probably there is no such thing as primary optic atrophy.

In actual fact, the appearance which has come to be familiar to us under the classification of secondary atrophy, is due to gliosis. In the primary form there is no gliosis. This gliosis may be brought about by any vascular disturbance, whether inflammatory as in papillitis, or circulatory as in papilledema. Where there is no vascular disturbance there is no gliosis.

Unfortunately, for those who like to classify things another variable may affect the picture. The tissue reaction, in this case gliosis, varies from person to person for a given amount of vascular disturbance, and is less

the farther back in the optic nerve it occurs.

Thus, following papillitis and papilledema in some cases, there may be little gliosis, and the nervehead which should have the appearance of secondary atrophy actually simulates the primary type. Such confusions are common in the experience of all ophthalmologists.

It is not difficult to understand, then, the ultimate confusion in the student's mind when he is confronted with a patient who has what looks like primary optic atrophy (when he knows that all cases of atrophy are really secondary), and then is told that this is actually a case of secondary atrophy (even though there is no gliosis) because the atrophy has followed upon papilledema.

Anyone who has been brought up in the old school can find his way through this confusion and can see a certain value in retaining the old terms. But, it must be admitted, in all fairness, that this value is minor. The confusion caused in the student's mind offsets any small advantage.

It is urged that the terms be given up. As a reasonable substitute, one might suggest the terms—atrophy without gliosis and atrophy with gliosis. These terms from the point of view of morphology and pathogenesis are more correct and thus much less confusing to the student.

John V. V. Nicholls.

CORRESPONDENCE

Optic nerve sheath hemorrhage

Editor,

American Journal of Ophthalmology:

The Jackson Memorial Lecture by F. B. Walsh and T. R. Hedges in the April, 1951, issue of the Journal needs some comment. At the XVIth International Congress of Ophthalmology in London,* I showed (with the collaboration of Dr. J. F. Hampe) by means of serial longitudinal and cross sections of the optic nerves from the pituitary up to the eye in three cases of spontaneous subarachnoid hemorrhage, that there really exists an open communication between the intracranial subarachnoid space and the subarachnoid spaces of the optic nerves in the orbit.

It became obvious from these sections that the blood in cases of spontaneous subarachnoid hemorrhage can be pressed through this open communication into the intervaginal spaces of the optic nerves. This sometimes happens with such a force that intradural hemorrhages occur, originating from the subdural space, as is proved by the ruptured innermost layers of the dura. In one of the cases at the time described by me in *Acta Ophthalmologica* **22**:281-299, 1944, the central retinal vein was almost torn to pieces, due to the sudden widening of the intervaginal spaces.

Walsh and Hedges are ardent supporters of the view of Ballantyne, who found hemorrhages among all tissues of the orbit and surrounding the vessels of the chiasma and optic tracts and who wrote that these hemorrhages "can only be explained by a sudden rise of intracranial pressure causing a stasis in all the venous channels which drain the tissues of the eye and the contents of the orbit."

Neither Ballantyne nor Walsh and Hedges realized, however, the many anastomoses of the veins in the orbit with the facial vein—the supraorbital, the angular, and the deep facial veins, and the pterygoid plexus (see fig. 249, of the third edition of *The Anatomy of the Eye and the Orbit* by E. Wolff).

It is clear that a sudden rise of intracranial pressure never can produce a stasis in all the venous channels which drain the tissues of the eye and the contents of the orbit. Therefore, it is far from being established beyond question "that the presence of increased venous pressure which is transmitted from the cranial cavity to the orbital veins is established beyond question. The degree and extent of venous ruptures are

* Proc. XVI Int. Congress of Ophth., London, 1:356-368, 1950.

dependent on the rapidity of onset and the magnitude of elevation of venous pressure in the brain and orbit," as Walsh and Hedges write.

Brückner (Schweiz. med. Wchnschr., **78**:355, 1948, and Ophthalmologica, **118**: 607, 1949) has stressed the fact that the ophthalmic artery is the only branch of the internal carotid that, immediately after its intracranial origin, carries off its blood to an extracranial area. This area is, in contrast to that of all other branches of the internal carotid, not submitted to the intracranial hypertension and therefore the ophthalmic artery will carry off, in cases of spontaneous subarachnoid hemorrhage, more blood than is usual.

The acute plethora of the ophthalmic artery also refers to the central retinal artery and its other branches in the orbit. Since small recurrent branches pass back through the superior orbital fissure or run back in the dural sheath of the optic nerve, arterial overfilling rather than venous stasis can more satisfactorily explain the hemorrhages throughout the whole orbit, and even the rare multiple hemorrhages behind the optic foramen.

The intraocular hemorrhages are due to ruptures in the retinal veins, as these veins cannot absorb the blood supplied from two sides; namely, (1) The venous congestion due to the sudden closure of the central vein where it traverses the intervaginal spaces, and due to the back-pressure of the venous blood in the neural part of the vein as the optic nerve itself is also compressed by the high intervaginal pressure, and (2) the overfilling of the central retinal artery.

Microscopic pictures of these ruptures were published by me in 1944 in the paper already referred to (Acta Ophth., **22**:281-299, 1944).

We were able to demonstrate in London the open communication through the optic canal, in addition to our anatomic examinations of cases of spontaneous subarachnoid hemorrhage, in a quite different manner.

With the aid of a neurosurgeon a mixture of gelatin (five percent) and India ink was injected suboccipitally into the subarachnoid space of human cadavers.

The cadaver was left face down for some hours after the injection. The next morning the optic canal and the optic nerve were cut out and, in some of the serial sections, the India ink could be traced through the whole length of the subarachnoid space in the optic canal.

It seems to me rather unlikely that the India ink came into the subarachnoid space of the intraorbital part of the optic nerve of these cadavers through "venous ruptures which are dependent on the rapidity of onset and the magnitude of elevation of venous pressure in the brain and orbit."

(Signed) W. A. Manschot,
Rotterdam, The Netherlands.

BOOK REVIEWS

THE EYE MANIFESTATIONS OF INTERNAL DISEASES. By I. S. Tassman, M.D. Saint Louis, C. V. Mosby Company, 1951, edition 3. 642 pages, 279 illustrations, 25 in color, index. Price: $12.00.

When an ophthalmic book by a living author runs into three editions, it is evidence that the book is a good one, the author knows his business, there is a continuous demand for it, and, finally, new material is sure to be presented. Those who are familiar with previous editions of *The Eye Manifestations of Internal Diseases*, will need little encouragement to purchase the present one.

Dr. Tassman, associate professor of ophthalmology, Graduate School of Medicine, University of Pennsylvania, is a good teacher, a skilled observer, and a fluent writer. The illustrations he has selected are exceedingly well chosen, although it must frankly be said that they are not always reproduced satisfactorily. Some of the black and white prints are blurred; this, perhaps, is the fault of neither author nor publisher,

but is due, in part, to the borrowing of pictures directly from other publications rather than using the originals or their dies. Many of the color illustrations are excellent, however.

There are 23 chapters, the first five having to do with the examination of the patient, the anatomy of the eye and orbit, and structural abnormalities. Then come an excellent chapter on congenital and hereditary eye manifestations and two valuable chapters on infections. Chapter 9 has to do with tuberculosis; 10, virus diseases; 11, fungus infections; 12, ocular parasites; 13, focal infections; 14, drug intoxications; 15, cardiovascular diseases; and 16, diseases of the blood.

Then follow chapters on disorders of menstruation and pregnancy, endocrine glands and metabolism, avitaminosis and diseases of nutrition (where it is unhappy to find that the author considers acne rosacea keratitis to be due to ariboflavinosis). The final chapters are on diseases of the nervous system, intracranial tumors, diseases of the skin, and diseases of the bones of the skull and orbit.

The subject matter is well arranged and much new material has been added. It is a book deserving an honored place in the physician's library.

Derrick Vail.

CONGENITAL GLAUCOMA. By J. Kluyskens. (Report presented to the Société Belge d'Ophtalmologie on February 26, 1950.) Brussels, Imprimerie Medicale et Scientifique (67, Rue de l'Orient), 1950.

The main object of this very comprehensive monograph on congenital glaucoma is to give a clear definition of the disease and similar anomalies and to summarize all the facts concerning its etiology, clinical manifestations, and treatment. The term, congenital glaucoma, was chosen because it expresses the symptomatology better than any other name—glaucoma because the hypertension is the cause for all the signs and symptoms, and congenital because a congenital malformation is the essential characteristic and cause of the disease.

The clinical observation comprises 214 cases; 31 of them being in patients of the author. They furnished the groundwork for this thorough and detailed study which covered all the phases of one of the most difficult problems in ophthalmology.

Congenital glaucoma is a malformation of the eyeball characterized by the persistence of an embryonic mesodermal tissue in the chamber angle, underdevelopment and retroplacement of the canal of Schlemm, and hypoplasia of the uvea, accompanied by enlargement of the cornea, deep anterior chamber, and, most important of all, increased intraocular pressure followed by corneal edema, tears in Descemet's membrane, stretching of the limbus and, finally, progressive optic atrophy.

One must distinguish between the complete and the incomplete forms, the congestive and the noncongestive types, and the early and late congenital glaucomas. The early congestive form is the most malignant. There is a very low percentage of familial occurrence, only 19 out of 214 cases. Exogenous and endogenous factors are more important for the etiology.

Special attention is given to the differential diagnosis which deals especially with megalocornea, juvenile glaucoma, and secondary glaucoma of young children.

Real megalocornea is an anomaly of structure. The cornea is enlarged, but clear and of normal curvature, and the limbus, iris, chamber angle, tension, and vision are normal. The anomaly is hereditary.

There also exists a megalocornea with preservation of an embryonic tissue in the chamber angle. This form should be considered to be an incomplete congenital glaucoma. The juvenile glaucoma is entirely different from the congenital glaucoma. It does not contain any abnormal tissue in the chamber angle and should be considered to

be a congestive or noncongestive glaucoma in a child or adolescent.

Secondary glaucoma follows uveitis, intraocular tumors, neurofibromatosis, microphthalmia and other congenital anomalies, but different from the anomalies of congenital glaucoma.

The only effective treatment is early surgery. The operations of choice were Elliot's trephining and iridencleisis. Perforating cyclodiathermy and surface cyclodiathermy gave promising results, especially in deformed eyes in which an opening of the eyeball would have been disastrous.

The goniotomies in this group include seven cases. Two cases from Dubois-Poulsen were unsuccessful. In four cases out of five operated on by Fieringa normal tension was achieved. Barkan had a normalization of the tension in 66 eyes out of 76. Gallenga's technique, namely the extraction of the lens, should be considered in secondary cataracts.

The surgical result in all the operations combined was favorable in 60 percent of the cases as far as the tension was concerned, but the vision could only be preserved in 23 percent. Still, if this is compared with the results of Jaensch in 1927, a considerable improvement in the control of a formerly hopeless condition was achieved.

The book is divided into nine well-arranged chapters. It contains many excellent illustrations and photomicrographs and much statistical data from the author's own as well as numerous other sources. It also contains a complete bibliography.

Alice R. Deutsch.

THE NEUROSES. By Walter C. Alvarez, M.D. Philadelphia, W. B. Saunders, 1951. Clothbound, 667 pages. Price: $10.00.

This distinguished author, who has spent much effort in recent years on emphasizing the importance of "diagnosing with the eyes and ears" rather than on purely laboratory findings, puts into print in this important book his experiences in the realm of functional disease.

The neuroses are commonly encountered in all phases of medical practice and certainly ophthalmology is no exception. The author states with justification that the majority of headaches have a neurotic basis. Since most patients with headaches are seen by the ophthalmologist, it is important that he recognize those that are not on the basis of ocular disease, refractive error, or muscular imbalance, and that he not add to the patient's functional state by placing upon him the burden of unwarranted glasses and future ocular fixation.

Also briefly mentioned are ocular hysteria, scintillating scotoma, the psychosomatic effects in the production of glaucoma, the care of the blind, and the psychic problems involved in incipient cataract and strabismus.

The book is divided into the following parts: (1) The need of a better recognition of the neuroses and minor psychoses; (2) diagnosis; (3) causes of neuroses and psychoses; (4) types of personality and several syndromes; (5) the psychosomatic features of the several specialties; (6) treatment.

While there may be some objection to portions of this book on the part of psychiatrists, it must be considered as a work by a nonpsychiatrist for other nonpsychiatrists who, perforce, must treat patients with neuroses. As such it has a great practical value. One is impressed with the common-sense approach of the author. Since there is related a multitude of interesting and illustrative case histories, the book makes rather fascinating reading. The author's personal experiences have perhaps caused overemphasis on migraine but this is understandable.

If it be true that nearly half the patients seen by ophthalmologists have some neurotic element which needs attention, then it is certainly important for ophthalmologists to read this book in its entirety.

William A. Mann.

ABSTRACT DEPARTMENT

EDITED BY DR. F. HERBERT HAESSLER

Abstracts are classified under the divisions listed below. It must be remembered that any given paper may belong to several divisions of ophthalmology, although here it is mentioned only in one. Not all of the headings will necessarily be found in any one issue of the Journal.

CLASSIFICATION

1. Anatomy, embryology, and comparative ophthalmology
2. General pathology, bacteriology, immunology
3. Vegetative physiology, biochemistry, pharmacology, toxicology
4. Physiologic optics, refraction, color vision
5. Diagnosis and therapy
6. Ocular motility
7. Conjunctiva, cornea, sclera
8. Uvea, sympathetic disease, aqueous
9. Glaucoma and ocular tension
10. Crystalline lens
11. Retina and vitreous
12. Optic nerve and chiasm
13. Neuro-ophthalmology
14. Eyeball, orbit, sinuses
15. Eyelids, lacrimal apparatus
16. Tumors
17. Injuries
18. Systemic disease and parasites
19. Congenital deformities, heredity
20. Hygiene, sociology, education, and history

6

OCULAR MOTILITY

Piper, H. F. **Types of strabismus and strabismus surgery.** Klin. Monatsbl. f. Augenh. **118**:33-51, 1951.

In horizontal strabismus, the author bases his choice of surgical procedure on the presence of adduction excess or abduction insufficiency. He attaches importance to the patient's age: an adduction excess below the age of 10 years later has a tendency to turn into abduction insufficiency due to the more or less fixed position of the globe. This does not apply to cases of genuine muscle paralysis, either congenital, or acquired in early childhood. Recession of the medial rectus (free tenotomy) is recommended in adduction excess; resection and advancement of the external rectus in abduction insufficiency. In combination of horizontal and vertical strabismus the horizontal deviation should be corrected first. Later, myectomy of the inferior oblique and, if necessary, recession of the inferior rectus on the other eye is recommended. He reports on eight cases of surgery of the vertical rectus muscles. (32 figures)

Theodore M. Shapira.

Sattler, C. H. **The treatment of strabismus with consideration of function.** Klin. Monatsbl. f. Augenh. **118**:22-23, 1951.

The importance of occlusion in cases of amblyopia exanopsia is stressed. Some results are claimed even at the age of 15 or 16 years. Surgery is advocated early when full correction of the refractive error and orthoptic exercises fail to correct the strabismus. Theodore M. Shapira.

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CONJUNCTIVA, CORNEA, SCLERA

Cogan, D. G., Allen, J. H., Calhoun, F. P., Jr., Dunphy, E. B., Swan, K. C., and Cordes, F. C. **Symposium: corneal diseases.** Tr. Am. Acad. Ophth. pp. 329-406, March-April, 1951.

Cogan, D. G. **Applied anatomy and physiology of the cornea.**

The newer concepts are well discussed. Epithelial healing depends primarily on regeneration or mitosis which occurs only in the two posterior layers. The duration of a single cell mitotic cycle is approximately 70 minutes, the duration of the resting stage about one week and there are 5,000 to 6,000 cells normally in mitosis at any one time. The cornea has a greater

capacity to swell than any other tissue. This is ascribed to a specific polysaccharid. In life, however, it is normally in a semi-pressed or deturged state, because of the continuous withdrawal of fluid from its anterior and posterior surfaces through osmosis. Corneal transparency is primarily due to this state of detergence, which maintains the necessary quantitative and qualitative fluid balance throughout its structure. Cloudiness is due to the reflections from multiple interfaces of substances of one refractive index suspended in a medium of a different refractive index.

Though water passes freely through the corneal epithelium and endothelium, these membranes are impermeable to solutes only soluble in water. The stroma is freely permeable to aqueous solutes. If the epithelium or endothelium is damaged, the hypertonic fluid on either side penetrates the stroma, with resulting swelling and opacification. Permeation of the entire cornea is possible only by solutes with a water- and a fat-soluble phase. This is true of most alkaloids. Avascularity is maintained largely through the corneas' state of deturgescence and absence of swelling. Marginal edema precedes new bloodvessel formation. Because of limbal resistance and greater compactness of the anterior stromal layers in corneal swelling, only the posterior surface is distorted. The two chief histochemical constituents of the cornea are collagen and a specific mucopolysaccharid. The former takes up water avidly but the latter takes up water only after the collagen requirements have been satisfied.

Allen, J. H. **Inflammation of the cornea.** pp. 360-365.

The fundamentals of such processes of inflammation as vascular dilation, permeability and new formation, fluid changes and cellular reactions are described as they occur in the cornea with its highly specialized structure and function. The epithelial lesions are described under the following headings: gray punctate opacities with or without staining, secondary superficial stromal involvement, epithelial keratitides, and epithelial erosions. Ulcerative lesions may be central, marginal and mixed. Superficial new bloodvessels are always preceded by edema and punctate opacities or infiltrations between Bowman's membrane and the epithelium. Acute necrosing stromal inflammations, diffuse necrosis or ring abcess are most frequently due to proteus bacillus infection, usually with trauma. Similar lesions, also with hypopyon, may be caused by septicemic plague, pneumonia and bacillus subtilis infections. Posterior abscess may be caused by trauma alone, but is usually associated with Moraxella lacunata or diplococcus pneumoniae infection. Disciform keratitis is usually due to trauma with infection; other causes are herpes simplex, vaccinia, varicella, and syphilis. Deep or stromal inflammations are usually central and accompanied by conspicuous vascularization. They may be due to syphilis, tuberculosis, leprosy or trypanomiasis. Among the causes of severe inflammations which damage or destroy the entire cornea are mustard gas, leprosy, and traumas with secondary infections.

Calhoun, F. P., Jr. **Degenerations and dystrophies.** pp. 366-381.

Degenerations are considered as retrograde changes in acquired tissues, and dystrophies in original or host tissues. The author classifies and discusses them according to their primary location. 1. Beginning at epithelial level are: keratitis sicca, keratomalacia and neuropathic keratopathy. 2. Beginning at or near the termination of Bowman's membrane are: pterygium, band keratopathy, white rings of Coats, white limbal girdle of Vogt, senile marginal degenerations, and arcs, both senile and juvenile. 3. Beginning in the central stroma are: Salzman's nodular dystrophy, the hereditary dystrophies including the crumb type (Groenow 1), the

spotty type (Groenow 2), the reticular or lattice type, lipin keratopathy, Hurler's disease, and cornea farinata. 4. Beginning at the endothelial level are Hassal Henle bodies, endothelial dystrophy (cornea guttata), Fuchs's epithelial dystrophy, and bullous keratopathy. The stages in the development of pterygium are: 1. deposit of lipin substances in the subconjunctival tissue (pinguecula); 2. hyperplasia and hyaline changes; 3. edema and focal infiltration at the limbus; 4. separation of Bowman's membrane from the epithelium; 5. ingrowth of conjunctiva and vessels.

In familial dystrophies no transitional or combined forms exist, one form does not change to another, and each type is transmitted through heredity only in its pure form, and is not associated with any known bodily abnormality. In the crumb type vision remains good until middle life, corneal sensitivity is only slightly diminished, and transmission is dominant. In the spotty type, vision is decreased early in life, sensitivity is greatly diminished, and transmission is recessive. In the lattice type, vision is decreased early, corneal sensitivity is moderately decreased, and transmission is dominant.

Dunphy, E. B. **Classification of diseases of the cornea.** pp. 382-386.

The classification is presented in tabular form with brief comments which amplify the data. Each corneal disease is listed in one of seven categories. The author regards the classification as temporary. When more is known about the etiologic factors and the basic mechanisms involved, a simpler and more logical classification can be made.

Swan, K. C. **Treatment.** pp. 387-400.

For the maximal effectiveness of conjunctivally instilled drugs the solution should flow down over the cornea. The viscosity of drug vehicles should be as high as practical. Wetting agents aid corneal permeability, they improve corneal epithelial contact, increase miscibility with the precorneal film and enhance epithelial permeability. The routine use of buffered solutions is unjustified. Changing the pH does not alter drug absorption but may reduce the associated irritability. Alkaloids and local anesthetics penetrate the cornea more rapidly in alkaline solutions. These are usually impractical because the free bases of these drugs are relatively unstable and insoluble in water. For maximal effectiveness, drug vehicles should have more affinity for the drug than the cornea so that the drug will penetrate the cornea and not remain in the vehicle. Drugs with a high oil affinity (fat soluble) if placed in oil and water mixtures, will concentrate in the oil more than the water and the reverse is true for highly water-soluble drugs. Therefore the latter should be administered in vehicles with low water solubility. Pencillin salts are highly water soluble and tend to remain in an aqueous solution rather than to penetrate the lipoprotein surfaces of the epithelial cells. They have a greater affinity for the epithelium than anhydrous bases therefore oily vehicles should be used with the penicillin salts, preferably in the form of a dry suspension. As the epithelium is the most important barrier to corneal permeability, its physical or chemical injury greatly increases the permeability of water-soluble drugs such as penicillin. Permeability may be increased by anesthetic instillation or massage.

In emergencies, more rapid adsorption of higher concentrations may be obtained with weak galvanic iontophoresis. Streptomycin chloride solutions with positive charge, move to the negative pole, but sodium sulphamerzin solutions, being negatively charged, will pass to the positive pole. With the latter the positive electrode is placed on the skin and the negative electrode in contact with the cornea. Perilimbal subconjunctival injection of water-soluble drugs also facilitates great-

er absorption, but violent reactions may ensue if the drug solution is too concentrated.

Of the sulpha drugs, sulphamerazine and sulphadiazene are preferred for systemic use and sulphacetamide for local use. No known antibiotic is effective for all infections and all antibiotics may cause allergic reactions. Antibiotics should not be used in the treatment of corneal inflammations unless 1. a specific diagnosis with reasonable certainty has been made, 2. the specific organism will respond to the specific antibiotic to be used, 3. the seriousness of the inflammatory condition justifies the use of antibiotics and 4. antibiotics will be administered effectively. Diagnosis by therapeutic response is usually a disservice to the patient. Sulphamylon in 0.5 to 1-percent aqueous solution is not inhibited by pus nor paraaminobenzoic acid. Penicillin solutions if used in effetive dosage and with an efficient technique will control most gram-positive cocci and pyogenic organisms and gram-negative cocci of the neisseria groups. Anhydrose suspensions are more effective than aqueous solutions if the corneal epithelium is intact, but if it is not intact, ointments potentially retard healing and minute droplets may be deposited subepithelially and act as foreign bodies. Penicillin hypersensitivity exists in from one to eight percent of all patients to whom the drug has been administered. In serious staphylococcus infections, penicillin susceptibility tests should be made for the specific organisms. Streptomycin and neomycin may be effective against some organisms which are resistant to penicillin and sulfonamides such as those of the hemophilus group and Bacillus pyocyaneus. In Morax-Axenfeld infections ointments should be applied to the lid margins and canthi as well as to the cornea.

Aureomycin is effective against most gram-positive and gram-negative organisms and in some virus infections. Locally it is best used in an anhydrous suspension (25 to 50 mg. in 5 cc.) or in ointment form. Properly administered it is usually well absorbed. The same is true of chloromycetin (chloramphenicol) and probably of terramycin. Bacitracin in ointment form should not be used if extensive epithelial defects exist. Only in the initial stages of allergic corneal infiltrations caused by food and drugs, is the systemic administration of antihistaminics helpful. Repeated use of wetting agents such as phemerol, zephiran, and sodium propionate, may produce epithelial opacities and erosions. ACTH and cortisone apparently have no curative effect and do not remove exogenous pathogenic factors in corneal inflammations. In uninfected corneal abrasions heat accelerates healing. In keratoconjunctivitis sicca, the treatment of associated hormonal imbalance, artificial tears preferably with a methyl cellulose base, condensation glasses, and permanent punctal closure, are advised.

Cauterization is generally deprecated. Marginal ulcers are frequently associated with metabolic deficiencies plus superimposed infections. In the staphylococcus type due primarily to blepharitis, persistent local treatment of the lids with or without toxoids or vaccines is frequently essential to success. The use of cortisone and sulphydryl compounds to minimize scar tissue formation in severe burns is still experimental. Local anesthetics should not be prescribed for home use. Foreign protein therapy should not be used in herpes of the cornea.

Cordes, F. C. **Summary and discussion.** pp. 401-406.

Among the important newer conceptions which have been presented are corneal deturgence in transparency, the epithelial barrier in drug penetration, and the epithelial-endothelial barriers to edema and neo-vascularization. Corneal inflammations are classified as 1. pseudo-inflammatory (degenerative), 2. incom-

plete inflammatory, 3. inflammatory. Degenerations have been primarily classified according to their initial two dimensional location (antero-posterior and lateral). Classification has been clarified and the structural and functional abnormalities that are seen clinically have been coordinated with pathologic processes and etiology. The following therapeutic concepts are emphasized: an efficient method of drug instillation, the value of wetting agents, the barrier role of the epithelium to drug penetration, the basic principles underlying the use of antibiotics and their application, the specific indications for several antibiotics, the treatment of keratoconjunctivitis sicca and other corneal-syndrome diseases. In advanced cornea guttata, cataract surgery may precipitate epithelial degenerative changes. In primary epithelial degenerations, pain and inflammatory reactions are more frequent than in stromal types. Superficial dystrophies are more amenable to lamellar keratectomy, stromal dystrophies to penetrating keratectomy. Chas. A. Bahn.

Forni, S. **Familial polymorphic degeneration of the posterior limiting membrane of the cornea.** Arch. d'opht. **11**:162-166, 1951.

Forni describes a group of alterations of the posterior limiting membrane (e.g., endothelium and Descemet's membrane combined) characterized by the presence of vesicles and fossettes. Some of the forms offer a superficial resemblance to cornea guttata but in the latter the prominences bulge into the anterior chamber whereas in the former the vesicles develop into fossettes which present a concave surface to the anterior chamber. In addition these alterations have a greater diameter than those in cornea guttata and are accompanied by deep stromal changes. Two cases are presented, one a man, 29 years of age, with a corrected vision of R. 0.7, L. 0.6, and the second, his son, a four-year-old boy with a vision of 1.0. It was not possible to examine any other members of the family. Both patients showed vesicles, fossettes, and irregular, deep, stromal opacities. Heredity seems to be dominant and the dystrophy appears early in life. It ordinarily does not have an important effect on visual acuity.

Phillips Thygeson.

Grom, Edward. **Papilloma of the cornea.** Klinika Oczna **19**:455-462, 1949.

The patient, a woman, 47 years of age, had third degree trachoma with pannus of the cornea and trichiasis. A papilloma starting from the limbus covered half of the cornea and was removed surgically.

Sylvan Brandon.

Mueller, H., and Maumenee, A. **Diseases of the corneal graft ("maladie du greffon").** Arch. d'opht. **11**:146-154, 1951.

Under the name "maladie du greffon", or "graft sickness", Paufique, Sourdille, and Offret described all the necrotic and opacification reactions of the corneal graft whose origin could not be determined clinically. Mueller and Maumenee review this and other monographs and pose the question of the possible allergic nature of these reactions. From a series of experimental researches they conclude that opacification of the graft is indeed due to sensitization of the recipient to the donor tissue. They show that in certain cases it is possible to block this allergic reaction by systemic use of ACTH or cortisone and by the use of cortisone topically. The general problems of keratoplasty and of hormonal therapy are discussed.

Phillips Thygeson.

Popkowski, J., and Golba, J. **Parinaud's disease.** Klinika Oczna **19**:351-363, 1949.

A case of this disease is presented. Extensive laboratory tests showed corynbacterium pyogenes, which belongs to the dyptheroid group as the exciting organism. Sylvan Brandon.

Stasinska-Misiurewicz, J. **Cancer of bulbar conjunctiva.** Klinika Oczna **19**: 449-453, 1949.

A case of cancer of the bulbar conjunctiva 7 mm. above the limbus is described. It appeared as a small tumor about 7 mm. in diameter. Microscopic examination revealed that it was carcinoma solidum. No other focus of cancer was found at that time but seven months later the patient died and the autopsy showed cancer of the breast with metastases in many other organs. Sylvan Brandon.

8

UVEA, SYMPATHETIC DISEASE, AQUEOUS

Czukrász, Ida. **Central serous chorioretinitis.** Ophthalmologica **121**:25-29, Jan., 1951.

A description of a typical case of the disease best known under the name of central spastic retinopathy is given.
Peter C. Kronfeld.

Lewenfiszowa, T., and Wilkowa, M. **Diagnostic tests in eye disease of rheumatic origin.** Klinika Oczna **19**:425-428, 1949.

Using the method described by Coburn and Paulis the authors found a certain factor "A" present in acute rheumatism and factor "B" in chronic rheumatism. Examinations of blood of scarlet fever patients disclosed the presence of factor "A" at the beginning and factor "B" in the following weeks of the disease. When serum containing factor "A" is placed over serum containing factor "B" a ring of cloudiness appears. Twenty-one cases of eye diseases, mostly iritis, were tested by this method. The presence of factor "A" corresponded to an acute iritis, and factor "B" to a chronic iritis. Positive results of the test suggest a rheumatic etiology of the iritis. Sylvan Brandon.

Sokolowski, Tadeusz. **Metaplastic ossification of the choroid and the retinal circulation.** Klinika Oczna **19**:439-447, 1949.

A case is described where an eye became blind after an injury that occurred 30 years ago and showed later symptoms of irritation. It was atrophic and blind. The eye was removed and an oval calcified shell with an opening for the optic nerve was found, which covered a large part of inside surface of the sclera. The author concluded that restricted circulation of the retina from one side and of the sclera from the other created favorable conditions for ossification of the choroid.
Sylvan Brandon.

9

GLAUCOMA AND OCULAR TENSION

Arkin, Wiktor. **The symptoms and the causes of acute hypotony of the eye.** Klinika Oczna **19**:413-418, 1949.

Acute hypotony is infrequent but occurs as the result of retinal detachment. The symptoms are: low tension, folds of the cornea, deepening of the anterior chamber, fogging of the media and change in color of the iris, all of which are due to the passage of fluid through the holes in the retina and into the vessels of the choroid. It does not occur spontaneously but usually after pressure on the eyeball.
Sylvan Brandon.

Francois, J. **The mode of action of the trephine operation.** Ophthalmologica **121**: 1-11, Jan., 1951.

The report deals with the gonioscopic findings in 27 glaucomatous human eyes on which trephining operations had been performed which resulted in normalization of the ocular tension. The inner aperture of the trephine canal was found to be obstructed by iris in 17 eyes, ciliary processes in 10 eyes and by a portion of the lens in one eye. Proliferation of the conjunctiva had closed off the opening in 10 cases. A filtering bleb was present in 22.

The author concludes that the trephining operation, like the iridencleisis, acts primarily by causing neurovascular modifications within the uvea. In his opinion trephining is not an appropriate technique for the production of an iris inclusion.

Peter C. Kronfeld.

Hebert, E. **Iridencleisis and its instrumentation.** Arch. d'opht. 11:172-173, 1951.

On the basis of his 150 cases since 1937, the author reports favorably on the iridencleisis operation in glaucoma. He employs the technique described by Weekers in 1934 but has developed a knife, manufactured by the Moria Company, for the ab externo incision. The knife blade is bent almost at right angles to the handle. The technique for performing an iridencleisis with this knife is described.

Phillips Thygeson.

Kapuscinski, W. J. **Magitot's theory of glaucoma.** Klinika Oczna 19:305-316, 1949.

Until recently, theories on glaucoma were accepting increased intraocular pressure as the most important cause. Magitot suggested that hypertension is only one of the symptoms which accompany the vasomotor disturbances located mostly in the thalamus, hypothalamus and hypophysis. Glaucomatous lesions of the optic nerve and of the visual field may appear without the presence of increased intraocular pressure. The author argues in favor of the correctness of Magitot's theory and describes his own experience, both clinical and experimental, which confirms the theory but also shows that there are certain forms of glaucoma which fall outside of its limits. He describes his work on provocative tests which appear to be of no value for diagnostic purposes and states that there is a basic difference between simple and acute glaucoma. The low readings of adaptation curves in individuals with glaucoma, the fact that the glaucomatous patients do not complain of hemeralopia, and the role of the hypothalamus in the metabolism of ocular pigment seem to confirm Magitot's theory. He discusses juvenile glaucoma and describes his own cases in which atropine decreased intraocular tension and pilocarpine increased it. This could not be explained on the basis of disturbances in the vegetative nervous system.

The cases of acute glaucoma, without increase of intraocular pressure and pigmentary dissemination, fell very well into the pattern of Magitot's concepts. The author concludes that there are obvious cases of optic nerve atrophy due to increased intraocular pressure which are not caused by disturbances of the subcortical centers. It is impossible to find one single etiological reason for all forms of glaucoma. Sylvan Brandon.

Madroszkiewicz, Marian. **Value of cyclodiathermy in surgical treatment of glaucoma.** Klinika Oczna 19:333-339, 1949.

The history and the method of clyclodiathermy according to Vogt is described. Indications for the use of cyclodiathermy are given and 20 operations are discussed. Eighteen eyes were relieved of pain; 17 out of 20 had the tension lowered to normal and in 3 it was lower than before the operation. No serious postoperative complications were encountered. Cyclodiathermy is effective in many cases when other operations give no satisfactory results. Sylvan Brandon.

11

RETINA AND VITREOUS

Järvi, O., and Oksala, A. **A case of retinal astrocytoma.** Ophthalmologica 121: 30-37, Jan., 1951.

An apparently benign retinal tumor from the eye of an 11-year-old girl proved to consist of mature glial cells. The occurrence of transitional cell forms sug-

gested that the tumor had originated from Müller's retinal glial cells.

Peter C. Kronfeld.

Miratynska-Ernestowa, E. **A case of Coats' disease.** Klinika Oczna **19**:419-424, 1949.

A case is described where the sight of the right eye in a woman, 45 years of age, was affected by a far advanced Coats' disease. There were posterior synechia, total retinal detachment, angiometosis of blood vessels, hemorrhages and glial hypertrophy. Extensive clinical investigation failed to reveal the cause. The author assumes that it might have been a focal infection. Sylvan Brandon.

Reynon. **Bilateral thrombosis of the central retinal vein.** Arch. d'opht. **11**:167-171, 1951.

Reynon reports the case of a 26-year-old soldier who suddenly lost the vision of the right eye, and two months later the vision of the left, due to thromboses of the central retinal veins. There was a history of old treated syphilis and the first ocular lesion followed a serological reactivation of the syphilis as a result of novarsenobenzol treatment. The thromboses are interpreted as Herxheimer reactions. Fundoscopic observations covering an 11-months period are reported; during this time the vision of the right eye returned to 10/10 and that of the left was limited to light perception only.

Phillips Thygeson.

Tumulty, P. A., Berthrong, M., and Harvey, A. M., **A peculiar pneumonia associated with retinal cytoid bodies.** Bull. Johns Hopkins Hosp. **88**:239-263, March, 1951.

Pneumonia in three patients was associated with retinal cytoid bodies. The disease began gradually and terminated in death from pulmonary insufficiency after many weeks. Fever, weight loss, malaise and cough were present. Cytoid bodies in the ocular fundi and moist basilar rales were the only significant physical findings. The white blood count remained normal. The etiology of the illness was not determined, but some features of a virus pneumonitis were present. In the first patient, a 35-year-old negro, cytoid bodies were not seen until two weeks after the onset of the illness, although ophthalmoscopic examination had been done at once. Later, hemorrhages and several cytoid bodies were seen in each fundus. In the second patient, a 55-year-old negro woman, numerous exudates and a few flame-shaped hemorrhages were found in both retinas. The third patient was a 64-year-old white woman who had numerous cytoid bodies in each fundus when first examined. (1 table, 19 figures, reference)

Bennett W. Muir.

13

NEURO-OPHTHALMOLOGY

Levinson, J. D., Gibbs, E. L., Stillerman, M. L., and Perlstein, M. A. **Electroencephalogram and eye disorders.** Pediatrics **7**:422-427, March, 1951.

One thousand two hundred and eighty-one children under 16 years of age were studied. Thirty percent of 36 children with strabismus, who were otherwise normal, had occipital abnormalities on the EEG. In children with organic brain disease causing cerebral palsy, electroencephalographic foci in the occipital region occurred almost twice as frequently in the presence of abnormal eye findings. This relationship prevailed regardless of the presence or absence of seizures. In patients with eye disorders, electroencephalographic foci involving the occipital region were six times more common than all other foci combined. On the basis of this study, it would seem that children who show some neuro-ocular disorder

should have a careful study of their EEGs for the possible detection of a central basis for the lesion. Conversely, patients who show an occipital focus on the EEG should have a thorough ophthalmologic examination to rule out eye abnormalities. (4 tables, references)

Bennett W. Muir.

15

EYELIDS, LACRIMAL APPARATUS

Arkin, W. **Conservative and surgical treatment of the lacrymal passages.** Klinika Oczna **19**:341-350, 1949.

Probing of lacrimal ducts should be limited to cases without dacryocystitis and should be used only occasionally. The lacrimal passages should not be slit. Dacryocystitis with patent lacrymal duct usually occurs when there is a temporary blockage of the lacrimal duct and distention of the sac. Treatment of blocked lacrimal passages in the newborn is discussed in detail. Toti's operation is used in cases with closed canaliculi. Adhesions in the canaliculus are broken during the operation from the side of the nose. If adhesions appear again probing is advised. Before cataract extraction dacryocystorhinostomy should be performed. Toti's operation as used by the author is discussed. Sylvan Brandon.

Drozdowska, Stanislawa. **Comparative treatment of marginal blepharitis.** Klinika Oczna **19**:367-381, 1949.

Seven tables are presented describing results of treatment on 81 patients. The most effective treatment consisted of local applications of penicillin, removal of infected lashes and touching the lid margin with 5 to 10-percent silver nitrate.

Sylvan Brandon.

Manchester, W. M. **A simple method for the repair of full-thickness defects of the lower lid with special reference to the treatment of neoplasms.** Brit. J. Plast. Surg. **3**:252-263, Jan., 1951.

When an eye is normal, the ideal repair should 1. replace skin, lashes, active muscle, tarsal plate and conjunctiva. 2. It should make use of local tissue only, that is, the skin should be eyelid skin, the lining should always be conjunctiva. 3. It should function normally. 4. It should produce a normal appearance, inflict no obvious damage on an upper lid which was normal before the repair began. 5. It should be certain. 6. It should be quick. 7. It should avoid the use of a blepharorrhaphy if a good result can be obtained without one.

For a total loss of the lower lid, Hughes' method is recommended, but three disadvantages are mentioned: a tendency to shortness of the new lid, occasional deformities of the upper lid, and, rarely, entropion of the upper lid. The author suggests modification of Hughes' procedure by dissecting the normal conjunctiva at the site of the excised tumor up from the fornix and away from the globe, even up to the limbus, and supplying an anterior lamina by the Tripier method of a bridge pedicle flap from the upper lid.

For partial full-thickness losses, Kollner's method of replacing the lining and supporting the partial defect by the use of a flap of conjunctiva together with a sector of the upper half of the tarsus of the upper lid is discussed. At a second stage the conjunctival bridge is divided, and the fissure reconstituted. The author suggests a combination of previously described techniques. A conjunctival flap corresponding in width to the defect is freed from the lower fornix and lower bulbar conjunctiva, and folded on itself to recreate the fornix at a higher level than that on each side. The flap is sutured in place, and for the anterior lamina, a double-pedicle flap of the Tripier type is

prepared on the upper lid, transposed to lie in the defect of the lower lid. The sutures which unite the upper border of the skin to the conjunctival flap and the lower border to the base of the lid are tied together over a tiny stint mold. The upper lid defect is closed by suture. The fate of each base of the flap is not discussed. The author points out that his new method avoids blepharorrhaphy, is quick and certain, but fails to replace active muscle, tarsus and lashes. (9 figures, 10 photographs) Alston Callahan.

Radnót, M., and Remenár, L. **Diagnosis of so-called prelacrimal tumors.** Klin. Monatsbl. f. Augenh. **118**:78-80, 1951.

Two cases are reported; in both, diagnosis was made roentgenologically before operation by injection of lipiodol. The first case was considered a diverticulum of the tearsac and was excised leaving the sac intact. The second was suggestive of a dermoid. The tumor, together with the superior posterior wall of the tearsac, was resected, and dacryocystorhinostomy was performed. Theodore M. Shapira.

16

TUMORS

Linoli, O., and Bocci, G. **Reticulosarcoma in the lacrimal sac region.** Boll. d'ocul. **30**:65-98, Feb., 1951.

A 64-year-old woman patient entered the Siena eye clinic for what seemed to be a bilateral peridacryocystitis. However, she had extensive painless lymphadenopathy and died 16 months after the onset of the disease, probably of abdominal metastases. Intensive X-ray therapy was of definite local effect only. The histological origin of the tumors could not be ascertained unequivocally. The importance of early biopsy is stressed; swollen lymph nodes should always arouse suspicion of malignancy, but the danger of propagation connected with any biopsy should not be underestimated. (3 clinical photographs, 8 microphotographs, more than 80 references) K. W. Ascher.

18

SYSTEMIC DISEASE AND PARASITES

Doret, M., and Röhm, A. **Ocular complications in benign leptospiroses (spirochetoses).** Klin. Monatsbl. f. Augenh. **118**:51-66, 1951.

In addition to Leptospira ictero-hemorrhagica, the spirochete that causes Weil's disease, a number of other spirochetes have been identified in recent years that are transmitted to man through intermediate hosts, and can be differentiated by agglutination tests. "Erntefieber" (harvest fever), "Canicola fever" (found in dogs, but also transmitted to man), and "Maladie des jeunes porchers" (disease of hog herdsmen) are examples.

These diseases are characterized by sudden onset of fever and severe headaches, only very rarely jaundice, slight albuminuria, and, the most typical sign, meningismus.

Ocular complications are more frequent in benign leptospiroses, and particularly in canicola fever, than has been supposed. They include conjunctivitis, iridocyclitis, choroiditis, neuroretinitis, papilledema, vitreous opacities, and retinal hemorrhages. None of these various manifestations is specific for one particular type of spirochete. In the eight cases examined two had papilledema directly related to meningeal disease; all others had iridocyclitis, in either a benign, rapidly healing form or a chronic form associated with vitreous opacities that caused a marked lessening of vision. They are membranelike with snowflake precipitates at various depths in the vitreous, of an appearance rarely seen elsewhere and of great diagnostic significance. In one case of benign leptospirosis a form of recurrent

iridocyclitis never before observed was seen. Theodore M. Shapira.

Pau, Hans. **Corneal dystrophy and cataract as sequelae of extirpation of the thyroid gland.** Klin. Monatsbl. f. Augenh. 118:75-78, 1951.

A 55-year-old woman had a thyroidectomy 11 years ago. Following the operation, severe tetanic attacks occurred that could be brought under control by adequate therapy. Six months later the vision gradually deteriorated to 1/18 in both eyes. The entire central stroma of both corneas was edematous and cloudy; the epithelium showed droplets of varying size; the stroma was traversed by dark stripes similar to water clefts; the corneal sensitivity was reduced and there were numerous fine pigment deposits on the posterior corneal surfaces. Both lenses showed net-like subcapsular opacities especially of the posterior cortices and the nuclei showed a milky white opacification. The eyegrounds could be seen with difficulty, and appeared normal. After 11 years the cataracts have not become mature (the decrease in visual acuity is mostly due to the corneal involvement) and the author believes that this is the result of successful therapy.

Theodore M. Shapira.

Straub, Wolfgang. **Toxoplasmosis with special considerations of the ocular symtomatology.** Klin. Monatsbl. f. Augenh. 118:66-75, 1951.

The morphology of toxoplasma and the clinical manifestations of toxoplasmosis in the newborn, the young, the adolescent, and the adult are discussed. Two percent of the population in Hamburg gave evidence of latent infections. The American and European literature is referred to.

Theodore M. Shapira.

19

CONGENITAL DEFORMITIES, HEREDITY

Harrison, S. H. **Treacher Collins syndrome.** Brit. J. Plast. Surg. 3:282-290, Jan., 1951.

Two cases of Treacher Collins syndrome are reported. The family history is variable, but there appears to be a distinct familial incidence. A comparison has been drawn between the Treacher Collins syndrome and unilateral facial agenesis. The embryology is discussed, and it is suggested that the causative factor may influence the development over a varying period, or by its concentration produce degrees of severity in the manifestations of this deformity. Alston Callahan.

Ophthalmic Miniature

In children tears do not flow at the first, but are induced by the effect of prolonged screaming, in gorging the vessels of the eye. This suffusion, leading at first consciously, and at last habitually, to the contraction of the muscles round the eyes, in order to protect or relieve them, the lachrymal glands become affected through reflex action. Thus, although in the first instance a merely incidental result, as purposeless as the secretion of tears from a blow outside the eye, or as a sneeze from bright light affecting the retina, we may understand how the shedding of tears serves as a natural relief to suffering.

Charles R. Darwin,
On the Expression of the Emotions in Man and Animals, 1872.

NEWS ITEMS

Edited by DONALD J. LYLE, M.D.
601 Union Trust Building, Cincinnati 2

News items should reach the editor by the 12th of the month but, to receive adequate publicity, notices of postgraduate courses, meetings, and so forth should be received at least three months before the date of occurrence.

DEATHS

Dr. Henry Alexander Beaudoux, Saratoga, California, died May 20, 1951, aged 79 years.

Dr. Lyman Copps, Marshfield, Wisconsin, died April 2, 1951, aged 61 years.

Dr. Linn Emerson, Orange, New Jersey, died April 17, 1951, aged 77 years.

Dr. Edward Bellamy Gresser, New York, died April 28, 1951, aged 53 years.

Dr. John James Prendergast, San Diego, California, died April 8, 1951, aged 45 years.

ANNOUNCEMENTS

GILL HOSPITAL SPRING MEETING

Among the guest speakers at the 25th annual spring congress of the Gill Memorial Eye, Ear, and Throat Hospital, Roanoke, Virginia, to be held April 7 through 12, 1952, will be: Dr. Francis Adler, Dr. Henry M. Goodyear, Dr. Hermann M. Burian, Dr. Bayard T. Horton, Dr. Paul A. Chandler, Dr. Howard P. House, Dr. John M. Converse, Dr. C. L. Jackson, Dr. Kenneth M. Day, Surgeon General Lamont Pugh, Dr. John H. Dunnington, Dr. Hunter H. Romaine, Dr. Edwin B. Dunphy, Dr. Frank B. Walsh, Dr. Watson Gailey, and Dr. James C. White.

WOMAN'S MEDICAL COLLEGE FELLOWSHIP

A two-year fellowship in ophthalmology has been added to the postgraduate training courses of the Women's Medical College, Philadelphia. Dr. Eunice LeBaron Stockwell is director of the fellowship, and the program will be carried out in the hospital of the Women's Medical College of Pennsylvania, the Women's Hospital, Pennsylvania School for the Deaf, and the Children's Heart Hospital. Dr. Marilyn Rigg, Los Angeles, is the first fellow to be selected.

UNITED KINGDOM TRANSACTIONS AVAILABLE

The Ophthalmological Society of the United Kingdom has a considerable stock of certain volumes of the *Transactions* since their first publication. The following years, however, are not available: 1897 through 1902; 1905 through 1912; 1917 through 1924; 1926 through 1939; 1944 through 1946.

The council would be glad to present to libraries, medical schools, and hospitals such available volumes as they may desire. No charge will be made other than for the cost of packing and postage.

Applications, which will be dealt with in rotation, should be addressed to the Honorary Secretary, Ophthalmological Society of the United Kingdom, 45 Lincoln's Inn Fields, London, W.C.2.

SOCIETIES

INSTITUTO PENIDO BURNIER

Officers of the Medical Association of the Instituto Penido Burnier, Campinas, São Paulo, Brazil, for 1951-1952 are. President, Dr. Leôncio de Souza Queiroz; 1st secretary, Dr. Milton B. de Toledo; 2nd secretary, Dr. Aloisio Af. Ferreira; treasurer, Dr. Roberto A. Barbosa; directors of the *Archives*, Dr. Penido Burnier, Dr. Guedes de Melo Filho, and Dr. F. J. Monteiro Sales.

DE SCHWEINITZ LECTURE

The 14th annual de Schweinitz Lecture of the College of Physicians of Philadelphia, Section on Ophthalmology, will be given on Thursday, November 15, 1951, at Philadelphia, by Dr. Peter C. Kronfeld, Chicago. The subject of Dr. Kronfeld's address will be "Tonographic studies of early glaucomas."

CENTRAL ILLINOIS MEETING

The next meeting of the Central Illinois Society of Ophthalmology and Otolaryngology will be held at the Dunlap Hotel, Jacksonville, Illinois, on September 21, 22, and 23. The guest speakers will be Dr. Theodore E. Walsh, Saint Louis; Dr. James H. Allen, New Orleans; and Mr. Henry C. Black, Detroit.

PERSONAL

At the International Congress of Industrial Medicine held in Lisbon, Portugal, September 9 to 15, Dr. Hedwig S. Kuhn, Hammond, Indiana, was a delegate from the American Academy of Ophthalmology and Otolaryngology and from the National Society for the Prevention of Blindness. Dr. Kuhn presented a paper before the Section on Industrial Ophthalmology during the congress.

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